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ORIGINAL ARTICLE

International Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility (iNEST): enrollment and methods

Joseph B. Stanford [1,2,3,*], Tracey Parnell[2,4], Kristi Kantor[2], Matthew R. Reeder[1], Shahpar Najmabadi [1], Karen Johnson[1], Iris Musso[1], Hanna Hartman[1], Elizabeth Tham[5], Ira Winter[6], Krzysztof Galczynski[7], Anne Carus[6], Amy Sherlock[8], Jean Golden Tevald[8], Maciej Barczentewicz[9], Barbara Meier[10], Paul Carpentier[10], Karen Poehailos[11], Robert Chasuk[12], Peter Danis[13], and Lewis Lipscomb[14]

[1]Office of Cooperative Reproductive Health, Department of Family and Preventive Medicine, University of Utah School of Medicine, Salt Lake City, UT, USA [2]International Institute for Restorative Reproductive Medicine, London, UK [3]University of Utah Sugarhouse and South Jordan Health Centers, Salt Lake City, UT, USA [4]Department of Family Practice, University of British Columbia, Vancouver, BC, Canada [5]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada [6]Life FertilityCare UK, Leamington Spa, UK [7]Faculty of Medical Sciences and Health Sciences, Siedlce University of Natural Sciences and Humanities, Siedlce, Poland [8]MorningStar Family Health Center, PC, Clinton, NJ, USA [9]Macierzyństwo i Życie Przychodnia Specjalistyczna, Lublin, Poland [10]In His Image Family Medicine, Gardner, MA, USA [11]First Med, Charlottesville, VA, USA [12]Family Health Center, Baton Rouge General Physicians, Baton Rouge, LA, USA [13]Mercy Clinic Family Medicine, St Louis, MO, USA [14]Novant Health Triad Obstetrics & Gynecology, Winston-Salem, NC, USA

*Corresponding author. Department of Family and Preventive Medicine, University of Utah School of Medicine, 375 Chipeta Way, Suite A, Salt Lake City, UT 84108, USA. E-mail: joseph.stanford@utah.edu https://orcid.org/0000-0002-9932-3947

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STUDY QUESTION: What is the feasibility of a prospective protocol to follow subfertile couples being treated with natural procreative technology for up to 3 years at multiple clinical sites?

SUMMARY ANSWER: Overall, clinical sites had missing data for about one-third of participants, the proportion of participants responding to follow-up questionnaires during time periods when participant compensation was available (about two-thirds) was double that of time periods when participant compensation was not available (about one-third) and follow-up information was most complete for pregnancies and births (obtained from both clinics and participants).

WHAT IS KNOWN ALREADY: Several retrospective single-clinic studies from Canada, Ireland and the USA, with subfertile couples receiving restorative reproductive medicine, mostly natural procreative technology, have reported adjusted cumulative live birth rates ranging from 29% to 66%, for treatment for up to 2 years, with a mean women's age of about 35 years.

STUDY DESIGN, SIZE, DURATION: The international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility (iNEST) was designed as a multicenter, prospective cohort study, to enroll subfertile couples seeking treatment for live birth, assess baseline characteristics and follow them up for up to 3 years to report diagnoses, treatments and outcomes of pregnancy and live birth. In addition to obtaining data from medical record abstraction, we sent follow-up questionnaires to participants (both women and men) to obtain information about treatments and pregnancy outcomes, including whether they obtained treatment elsewhere. The study was conducted from 2006 to 2016, with a total of 10 clinics participating for at least some of the study period across four countries (Canada, Poland, UK and USA).

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PARTICIPANTS/MATERIALS, SETTING, METHODS: The 834 participants were subfertile couples with the woman's age 18 years or more, not pregnant and seeking a live birth, with at least one clinic visit. Couples with known absolute infertility were excluded (i.e. bilateral tubal blockage, azoospermia). Most women were trained to use a standardized protocol for daily vulvar observation, description and recording of cervical mucus and vaginal bleeding (the Creighton Model FertilityCare System). Couples received medical and sometimes surgical evaluation and treatments aimed to restore and optimize female and male reproductive function, to facilitate *in vivo* conception.

MAIN RESULTS AND THE ROLE OF CHANCE: The mean age of women starting treatment was 34.0 years; among those with additional demographic data, 382/478 (80%) had 16 or more years of education, and 199/659 (30%) had a prior live birth. Across 10 clinical sites in four countries (mostly private clinical practices) with family physicians or obstetrician–gynecologists, data about clinic visits were submitted for 60% of participants, and diagnostic data for 77%. For data obtained directly from the couple, 59% of couples had at least one follow-up questionnaire, and the proportion of women and men responding to fill out the follow-up questionnaires was 69% and 67%, respectively, when participant financial compensation was available, compared to 38% and 33% when compensation was not available. Among all couples, 57% had at least one pregnancy and 44% at least one live birth during the follow-up time period, based on data obtained from clinic and/or participant questionnaires. All sites reported on female pelvic surgical procedures, and among all participants, 22% of females underwent a pelvic diagnostic and/or therapeutic procedure, predominantly laparoscopy and hysterosalpingography. Among the 643 (77%) of participants with diagnostic information, ovulation-related disorders were diagnosed in 87%, endometriosis in 31%, nutritional disorders in 47% and abnormalities of semen analysis in 24%. The mean number of diagnoses per couple was 4.7.

LIMITATIONS, REASONS FOR CAUTION: The level of missing data was higher than anticipated, which limits both generalizability and the ability to study different components of treatment and prognosis. Loss to follow-up may also be differential and introduce bias for outcomes. Most of the participating clinicians were not surgeons, which limits the opportunity to study the impact of surgical interventions. Participants were geographically dispersed but relatively homogeneous with regard to socioeconomic status, which may limit the generalizability of current and future findings.

WIDER IMPLICATIONS OF THE FINDINGS: Multicenter studies are key to understanding the outcomes of subfertility treatments beyond IVF or IUI in broader populations, and the association of different prognostic factors with outcomes. We anticipate that the iNEST study will provide insight for clinical and treatment factors associated with outcomes of pregnancy and live birth, with appropriate attention to potential biases (including adjustment for potential confounders, multiple imputation for missing data, sensitivity analysis and inverse probability weighting for potential differential loss to follow-up, and assessments for clinical site heterogeneity). Future studies will need to either have: adequate funding to compensate clinics and participants for robust data collection, including targeted randomized trials; or a scaled-down, registry-based approach with targeted data points, similar to the multiple national and regional ART registries.

STUDY FUNDING/COMPETING INTEREST(S): Funding for the study came from the International Institute for Restorative Reproductive Medicine, the University of Utah, Department of Family and Preventive Medicine, Health Studies Fund, the Primary Children's Medical Foundation, the Mary Cross Tippmann Foundation, the Atlas Foundation, the St. Augustine Foundation and the Women's Reproductive Health Foundation. The authors declare no competing interests.

TRIAL REGISTRATION NUMBER: The iNEST study is registered at clinicaltrials.gov, NCT01363596.

Key words: subfertility / infertility / restorative reproductive medicine / practice-based research / cohort studies / ovulation / luteal phase

WHAT DOES THIS MEAN FOR PATIENTS?

Subfertile (infertile) couples and their clinicians have a variety of treatment options to consider when seeking a live birth. One treatment approach is natural procreative technology, a specific type of restorative reproductive medicine, which is based on the Creighton Model FertilityCare System. However, all studies published to date about outcomes of natural procreative technology have been based in single medical practices, which may have somewhat limited information.

The international Natural Procreative Technology Evaluation and Surveillance of Treatment (iNEST) was conducted in 10 different clinics in four different countries, from 2006 to 2016, to get detailed information about which couples are treated, how many couples continue treatment, the components of the evaluation and treatment, and how many couples have a pregnancy or a live birth. We also sought to learn what other evaluation or treatments couples sought before, after or during their treatment with natural procreative technology. We collected information from the clinics, and also directly from the patients with follow-up questionnaires. The purpose of this report was to present the feasibility of the iNEST protocol and completeness of the information obtained. We found that the average age of women being treated was 34 years, 80% of women had 16 or more years of education, and 30% had one or more prior births. Among all couples, 57% had at least one pregnancy and 44% at least one live birth during the follow-up time period, based on data obtained from clinic and/or participants. The completeness of information varied across the clinics. When women and men received financial compensation for the follow-up questionnaires, they were much more likely to respond, indicating that compensating patients is necessary to get information beyond what can be obtained from clinic records. We expect that the iNEST study will help us understand which couples and treatment components are most likely to result in a live birth. Future multiclinic studies can learn from our experience to conduct similar studies.

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Introduction

Subfertility, commonly called infertility, is usually defined as seeking unsuccessfully to conceive for 1 year or more (Farquhar *et al.*, 2019). It is part of a spectrum of couple fecundability (Dunson *et al.*, 2002), and when the woman is 35 years or more, the time cut-off used to define subfertility is usually 6 months rather than 1 year (American Society for Reproductive Medicine, 2020). It affects at least 15% of couples during their reproductive lifetime (Oakley *et al.*, 2008; Crawford *et al.*, 2015). Recurrent miscarriage has been defined at least two losses of clinically recognized pregnancies before fetal extrauterine viability (American Society for Reproductive Medicine, 2020), and under this definition, affects about 1.9% of women of reproductive age (Quenby *et al.*, 2021). One of the key issues for research and policy is to determine the appropriate level of intervention for each couple seeking a live birth, to avoid undertreatment or overtreatment (Fields *et al.*, 2013; Kersten *et al.*, 2015; Eijkemans *et al.*, 2017). The majority of clinical outcomes research for fertility treatment focuses on IVF and related techniques of ART; however, ART is not required for most subfertile couples to conceive (Boltz *et al.*, 2017; Righarts *et al.*, 2017; Annual Capri Workshop Group, 2019). In addition, some couples do not wish to use IVF, or cannot afford it (van Weert *et al.*, 2007; ESHRE Capri Workshop Group, 2015).

Restorative reproductive medicine is an umbrella term for approaches to treatment that seek to restore or support underlying reproductive function and fertility in support of natural conception, without the use of IVF or IUI (Boyle *et al.*, 2018). Natural procreative technology (NaProTechnology) is a specific type of restorative reproductive medicine, developed for couples who are using the Creighton Model FertilityCare System (CrM; Hilgers, 2004). Natural procreative technology has medical and surgical protocols; this study focused on the use and outcomes of the medical protocols. With the CrM, women observe and chart biomarkers of ovulation and hormone function during the menstrual/ovulation cycle based on daily observations of vaginal discharge (resulting from uterine bleeding and cervical mucus production; Hilgers and Prebil, 1979). Clinicians work with the woman and couple to provide medical evaluation and support, informed in several ways by the CrM. 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, particularly relevant for subfertile couples who may have a narrow fertile window (Stanford *et al.*, 2003; Keulers *et al.*, 2007). This increases awareness of intercourse timing and cycle health for the couple. Second, the cervical mucus peak day is an efficient way to track the timing of ovulation, relevant to certain diagnostic tests, such as midluteal assessments (Fehring, 2002; Stanford *et al.*, 2020b), and also for timing some treatments, such as ovulation stimulation drugs or ovulation trigger shots. Third, cervical mucus patterns provide direct insight into fecundability (Marshell *et al.*, 2021). Fourth, when the clinician employs medications or surgical interventions to stimulate ovulation and/or support the hormonal function of the menstrual/ovulation cycle, the CrM chart can be used as a tool to assess the response to treatment (Tham *et al.*, 2012).

Formal evaluation of the outcomes of natural procreative technology and other restorative approaches in medical practice has been limited to a few studies based on single medical practices (Stanford *et al.*, 2008, 2021; Tham *et al.*, 2012; Frank-Herrmann *et al.*, 2017; Boyle *et al.*, 2018). The international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility and Miscarriage (iNEST) study is a multinational prospective observational study designed and conducted to assess the implementation and outcomes of natural procreative technology in multiple populations and settings, and the characteristics of patients that may correlate with the likelihood of live birth with treatment. The purpose of this article is to describe the study design, data sources, enrollment and the data collected for this study. We also describe the level of response for follow-up in relation to compensation of participants, and the validity of self-reported pregnancy outcomes compared to medical records.

Materials and methods

Overview of iNEST

The iNEST study is a prospective multiclinic, multinational study, which enrolled couples who presented seeking to become pregnant or maintain a pregnancy. Participating clinics and clinicians were physicians, and their associated clinicians (midwives, physician assistants), who were trained in medical natural procreative technology (Hilgers, 2004). There were no clinicians in this study who were trained in surgical natural procreative technology. The two main aims of the study were: to determine the live birth rate over time for patients treated with medical natural procreative technology for subfertility or history of spontaneous abortion; and examine how the live birth rate varied by patient characteristics, especially the age of the woman, prior pregnancy, time attempting to conceive, underlying diagnoses and adherence with evaluation and treatment. The iNEST study began in 2006 with four clinical sites and grew to include 10 clinical sites in four countries by the end of the study. The last enrollment was December 2016. We attempted to follow all couples for 3 years after entering the study, regardless of whether they continued treatment.

Study design

The design of iNEST was a prospective longitudinal cohort study enrolling couples from existing clinical practice sites; no therapeutic interventions were directed by study. Couples presenting for possible treatment with natural procreative technology were recruited to participate in the study. Data were collected in the following ways:

- The written informed consent form (paper form) included the woman's and man's birth dates. A signature was required from both the woman and the man, in order for a couple to enroll in the study. In some cases, the consent document was read and signed online, after which the potential study participant was contacted by a staff member to discuss any questions and to further explain the study.
- Entrance questionnaires were obtained from participating couples (separate questionnaires for women and men) at entry through the clinical practice site.
- Follow-up questionnaires were sent by iNEST study staff or, in some cases, the clinical practice site. We sought to contact participants to complete a follow-up questionnaire on an annual basis for up to 3 years, and upon exit from the study. In some cases, a participant completed a combined yearly follow-up and exit

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questionnaire. Follow-up questionnaires were sent regardless of whether the couple was known to have conceived, and/or known to have continued in contact with the clinical practice site. All follow-up questionnaires had a separate version for the woman and the man. These questionnaires included questions about all types of treatments the couple had received, including natural procreative technology, ART, or alternative treatments (e.g. acupuncture), and whether treatments were received from the original natural procreative technology clinic or elsewhere.

- Whenever a pregnancy was identified by the woman, the man or the clinical site, we asked the woman to complete a pregnancy questionnaire.
- Couples provided copies of the CrM charts for data abstraction. The CrM system includes a daily diary of fertility biomarkers including vaginal bleeding, vaginal discharge from cervical fluid (mucus), intercourse and medications taken (Hilgers, 2004). These charts were provided as PDF documents to the study coordinating center, where they were abstracted by coordinating center research staff.
- Medical record abstraction was also performed periodically in each clinical practice site by the clinician or another designated person. Some clinics performed their medical record abstraction on site and entered the data into a secure online interface built for this study. Other clinics abstracted medical record data into document templates, which were faxed or securely sent by email to the data coordinating center (University of Utah), where the data were entered into the database by central study personnel. Elements abstracted included diagnoses, medical treatments, surgeries, pregnancies and pregnancy outcomes.

Questionnaires were administered through a secure online platform (Opinio or Qualtrics) or completed on paper.

Eligibility

Couples eligible for the study included all couples who were considering natural procreative technology treatment to help them achieve a live birth, and who presented to participating physicians or other providers during the enrollment period. For the purposes of this study, all couples receiving medical assistance with natural procreative technology for the purposes of seeking or maintaining pregnancy were eligible for enrollment. There was no requirement for a specific time trying to conceive prior to treatment. A couple was excluded if either partner was <18 years of age, or if the couple had absolute infertility (e.g. bilateral tubal blockage, azoospermia). Participating clinical practice sites were in Canada (Toronto), Poland (Lublin), the UK (Leamington Spa) and the USA (Louisiana, Massachusetts, Missouri, New Jersey, North Carolina, Utah and Virginia). In all participating clinical sites, physicians with formal training in medical natural procreative technology offered treatment for subfertility or miscarriage. Some practices also had other clinicians providing clinical care, including midwives, nurse practitioners or physician assistants. These clinics from different countries and geographic areas were recruited to provide a broad representation of couples receiving natural procreative technology, and also based on willingness of the clinics to participate. The study coordinating center was based at the University of Utah, Department of Family and Preventive Medicine, Division of Public Health, Office of Cooperative Reproductive Health.

Primary outcome

The main outcome for this study is the proportion of subjects who had a live birth at various time points during the 3 years of follow-up after their first consult for treatment with natural procreative technology, compared to couples who did not receive natural procreative technology treatment, or who ceased to receive natural procreative technology treatment, but continued to respond to follow-up questionnaires.

Outcomes for this report

The outcomes for this report were descriptive, including enrollment of eligible participants by site, characteristics of participants, clinical diagnoses, completion of data instruments (including by compensation status), related surgeries and, for one site, comparison of birth outcomes reported by questionnaire versus obtained from medical records.

Descriptive variables

Demographic characteristics

Maternal age was defined at study enrollment and calculated by subtracting woman's date of birth from woman's consent date. Maternal race/ethnicity, marital status, household income and maternal education were based on self-reported responses to questions asked on the entrance questionnaire, or from information collected at enrollment.

Reproductive characteristics

The woman's entrance questionnaire had questions about reproductive characteristics, including prior pregnancy, prior live birth, prior fertility treatments, prior surgeries and time trying to conceive. To determine time trying to become pregnant, both women and men were asked to indicate the month and year that they began trying to have a baby (defined as sexual intercourse without any contraception or family planning method to avoid pregnancy), and the earliest reported date from the two partners was subtracted from the date of entering the study. During the study, we found that some couples were not completing the entrance questionnaire, so we added questions about time trying, prior pregnancies and prior fertility treatments to the informed consent document. We used data from both sources for this analysis.

Previous diagnoses—women and men

Women and men participants were asked on their respective entrance questionnaires to mark all fertility-related diagnoses that they have ever been told or suspected that they have.

Diagnoses

Diagnostic data were provided by the clinics, not the participants. A set list of diagnoses was provided, and clinics were asked to indicate whether each diagnosis applied to each couple (yes or no), for at least at one point during the study.

Clinic visits

Data on clinic visits were provided by the clinics, not the participants. Clinics were asked to enter the date of each visit, whether the woman or the man was present, or both, and whether the visit was full length or abbreviated (e.g. a visit for follicular ultrasound).

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Creighton Model FertilityCare chart

Most participating clinics obtained scanned or photographed images of the CrM charts (daily diaries) of participating couples.

Clinical interventions

In the follow-up questionnaires, women and men reported on clinical interventions they had received, either from the study clinical site or from any other clinic or source. Women reported on medications they were taking, either from the natural procreative technology clinic or from any other clinic or source. Medication information was also retrieved from the CrM chart. Reproductive surgeries and procedures performed on participants during the study were reported by the clinics. A set list of surgical procedures was provided, and clinics were asked to indicate whether each woman and each man participating in the study had each surgery, and if so, the dates. In addition, surgeries were also reported by participants on their follow-up questionnaires.

Pregnancies and outcomes

Pregnancies and their outcomes were reported by participants on follow-up questionnaires, including positive home pregnancy tests and pregnancy ultrasounds, and also separately by clinics from medical record abstraction, as confirmed by clinicians in the medical record. From both sources, the date of the last menstrual period, the estimated date of conception (based on the CrM chart), and the clinically identified due date were recorded.

Compensation

Clinics and clinicians were not compensated for participating in the study. During part of the study when funding was available, participants were compensated for completing participant yearly follow-up questionnaires, end-of-study questionnaires and/or pregnancy questionnaires. Starting in February 2015, when funding was no longer available to compensate participants owing to the end of grant funding, participants were informed that no funding was available, but still invited to complete surveys without compensation. This provided an opportunity to compare completion rates of surveys with and without compensation, which we did for 1 year immediately before the change and 1 year immediately after.

Descriptive analysis of available data

Participants who had completed eight or more sections of the entrance questionnaire (out of 19 sections total for women and 16 sections total for men) were considered to have completed the questionnaire. For any follow-up questionnaire, individuals were included in the counts if they had a record of completing at least one of the following questionnaires: annual follow-up, pregnancy or exit questionnaire. Couples were determined to have any clinic visit data if they had a record with at least one visit in the natural procreative technology clinic visit table, and individuals with any diagnosis data were those who had diagnoses as recorded by their clinician during the study period. Pregnancy and live birth information during the study were collected from participants via follow-up questionnaires (i.e. annual follow-up, pregnancy and exit questionnaires), and also by the clinician. Pregnancy reports were compared, and duplicates eliminated. For this report, surgeries were abstracted from clinic reports only.

Study registration

The iNEST study is registered at clinicaltrials.gov: NCT01363596.

Ethics approval

The study was approved by the University of Utah Institutional Review Board, IRB #00014070. Each clinical site obtained research ethics approval from an IRB or Research Ethics Committee with jurisdiction for their site. Some private clinical practices relied on the University of Utah IRB review. From each couple participating in the study, both the woman and the man provided written informed consent. Most consents were completed on paper, but for some sites and some participants, consents were obtained electronically.

Results

Out of 2032 couples screened by natural procreative technology providers, 1668 (82%) were identified as eligible for the study and 834 (50.0%) enrolled into the study (Table I). The women's mean age was 34.0 years (range 19–47 years). For those for whom other demographic data were available (roughly half of participants), most had 16 or more years of education and relatively high and income (Table II).

Available data

About 65–80% of participants had various elements of reproductive history available. About 46% had a history of prior pregnancy, 33% did not and for 21% their pregnancy history was not available. About 7% had previously received IVF, 15% IUI and 36% ovulation drugs (Table III). The entrance questionnaire was completed by 58% of women and 48% of men, while clinic visit data were available for 60% of couples (Table IV).

Table I Patients who were screened, eligible and consented, by clinical site (iNEST 2006–2016).

	Screened	Eligible	Consented
Clinic	**N**	**n**	**n (%)[a]**
Canada	697	458	148 (32.3)
Poland	94	94	93 (98.9)
UK	352	352	186 (52.8)
USA/LA	67	67	21 (31.3)
USA/MA	182	152	51 (33.6)
USA/MO	19	18	18 (100.0)
USA/NC	10	10	10 (100.0)
USA/NJ	306	249	172 (69.1)
USA/UT	269	232	111 (47.8)
USA/VA	36	36	24 (66.7)
All	**2032**	**1668**	**834 (50.0)**

iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility; LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia.
[a]Percentage of identified eligible patients who consented to participate.

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Table II Characteristics of female participants, by clinical site (iNEST 2006–2016).

	Canada	Poland	UK	USA/LA	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All
	148	93	186	21	51	18	10	172	111	24	834
Age (years)											
Mean (range)[a]	33.5 (22–46)	32.1 (24–41)	36.5 (25–47)	32.2 (25–44)	34 (26–47)	33.5 (27–44)	35.2 (29–42)	34.9 (23–46)	32.3 (19–47)	32.3 (20–44)	34.0 (19–47)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Race/ethnicity											
White (non-Hispanic)	69 (46.6)	10 (10.8)	44 (23.7)	12 (57.1)	36 (70.6)	12 (66.7)	1 (10.0)	128 (74.4)	72 (64.9)	13 (54.2)	397 (47.6)
Asian (non-Hispanic)	13 (8.8)	0 (0.0)	3 (1.6)	1 (4.8)	1 (2.0)	2 (11.1)	0 (0.0)	12 (7.0)	4 (3.6)	0 (0.0)	36 (4.3)
Hispanic (any race)	5 (3.4)	0 (0.0)	1 (0.5)	0 (0.0)	2 (3.9)	0 (0.0)	1 (10.0)	13 (7.6)	9 (8.1)	1 (4.2)	32 (3.8)
Other	3 (2.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (2.0)	1 (5.6)	0 (0.0)	3 (1.7)	1 (0.9)	1 (4.2)	11 (1.3)
Missing	58 (39.2)	83 (89.2)	137 (73.7)	8 (38.1)	11 (21.6)	3 (16.7)	8 (80.0)	16 (9.3)	25 (22.5)	9 (37.5)	358 (42.9)
Marital status											
Not married	6 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.9)	0 (0.0)	8 (1.0)
Married	92 (62.2)	10 (10.8)	51 (27.4)	17 (81.0)	47 (92.2)	16 (88.9)	8 (80.0)	166 (96.5)	95 (85.6)	24 (100.0)	526 (63.1)
Missing	50 (33.8)	83 (89.2)	135 (72.6)	4 (19.0)	4 (7.8)	2 (11.1)	2 (20.0)	5 (2.9)	15 (13.5)	0 (0.0)	300 (36.0)
Household income (USD)[b]											
≤25 000	3 (2.0)	0 (0.0)	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	1 (0.9)	1 (4.2)	11 (1.3)
25 001–50 000	9 (6.1)	0 (0.0)	20 (10.8)	1 (4.8)	3 (5.9)	0 (0.0)	0 (0.0)	5 (2.9	17 (15.3)	0 (0.0)	55 (6.6)
50 001–75 000	16 (10.8)	0 (0.0)	5 (2.7)	4 (19.0)	4 (7.8)	2 (11.1)	0 (0.0)	24 (14.0)	22 (19.8)	1 (4.2)	78 (9.4)
75 001–100 000	15 (10.1)	0 (0.0)	19 (10.2)	2 (9.5)	5 (9.8)	0 (0.0)	0 (0.0)	39 (22.7)	9 (8.1)	2 (8.3)	91 (10.9)
>100 000	24 (16.2)	0 (0.0)	0 (0.0)	5 (23.8)	21 (41.2)	6 (33.3)	0 (0.0)	71 (41.3)	13 (11.7)	1 (4.2)	141 (16.9)
Missing	81 (54.7)	93 (100.0)	138 (74.2)	9 (42.9)	18 (35.3)	10 (55.6)	10 (100.0)	31 (18.0)	49 (44.1)	19 (79.2)	458 (54.9)
Education (years)											
≤12	8 (5.4)	0 (0.0)	4 (2.2)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	4 (2.3)	10 (9.0)	1 (4.2)	28 (3.4)
13–15	13 (8.8)	1 (1.1)	3 (1.6)	2 (9.5)	1 (2.0)	1 (5.6)	0 (0.0)	29 (16.9)	16 (14.4)	2 (8.3)	68 (8.2)
16–18	39 (26.4)	6 (6.5)	22 (11.8)	6 (28.6)	30 (58.8)	4 (22.2)	1 (10.0)	79 (45.9)	37 (33.3)	7 (29.2)	231 (27.7)
>18	32 (21.6)	2 (2.2)	20 (10.8)	5 (23.8)	9 (17.6)	9 (50.0)	1 (10.0)	44 (25.6)	24 (21.6)	5 (20.8)	151 (18.1)
Missing	56 (37.8)	84 (90.3)	137 (73.7)	8 (38.1)	11 (21.6)	3 (16.7)	8 (80.0)	16 (9.3)	24 (21.6)	9 (37.5)	356 (42.7)

LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia; iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.
[a]Excludes 36 missing dates of birth.
[b]Household income was dropped from the questionnaire during the study, based on feedback from some participants and clinics.

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During the study, 57% of women/couples had at least one pregnancy, and 44% had a least one live birth (Table V). Pregnancies were identified by the clinic only (105, 22.2%), by the participants in follow-up questionnaires only (32, 6.8%), or by both sources (336, 71.0%).

Approximately three-quarters of participants (77%, n = 643) had clinical diagnostic data available. Among the couples with diagnostic data, an ovulatory disorder was identified in 87%; among these, 77% had luteal insufficiency (based on luteal length or serial serum progesterone or estradiol levels), 31% low follicular estradiol levels and 27% had ovulatory abnormalities on follicular ultrasound. Endometriosis was identified in 31% and polycystic ovary syndrome in 24%. An abnormal semen analysis was identified for 24%. Reduced cervical mucus was identified in 55%. Other common associated diagnoses were premenstrual syndrome (42%), and female vitamin D deficiency (34%). Among couples with diagnostic data, the mean number of diagnoses per couple was 4.7 excluding female symptoms, and 6.0 including the female symptoms (premenstrual syndrome, abnormal bleeding, reduced cervical mucus; Table VI). In participant recall of diagnoses prior to the evaluation within the iNEST study, 22% of women reported a prior diagnosis of unexplained infertility, 8% reported a male factor diagnosis and fewer than 5% of men reported other male fertility diagnoses (Supplementary Tables SI and SII).

Clinical interventions

Information about medications was available for 391 (47%) of couples in the study. Among these, the most commonly prescribed medications (other than multivitamins and folic acid) were progesterone during the luteal phase (60%), medications to enhance cervical mucus production, including vitamin B6 (33%) or guaifenesin (27%), and medications to stimulate ovulation, principally clomiphene citrate (38%) or letrozole (32%; Table VII). About one-fifth (22%) of women had a pelvic surgery or procedure (including radiologic procedures) reported by the clinical site during the study. The most common procedure was laparoscopy (81% of women with any procedure), followed by hysterosalpingography (62%) and hysteroscopy (46%) (Table VIII).

Response rate for questionnaires

Because of changes in funding for the study, compensation to participants for completion of questionnaires was no longer available after mid-February 2015. We evaluated the completion rates for questionnaire for 1 year immediately before and 1 year immediately after this change. The completion/response rate for yearly follow-up questionnaires was about two-thirds for both women and men when compensation was provided, and about one-third for both women and men when compensation was not provided. However, the availability of compensation did not change the completion rate for pregnancy questionnaires (sent to pregnant women), which was about three-quarters for both time periods (Table IX).

Validation of questionnaire-reported pregnancy outcomes

To conduct a validation of the woman's pregnancy questionnaire, we conducted a source medical record review for 31 pregnancies at one of the sites (UT). These were consecutive pregnancies where the delivery or miscarriage was documented within the electronic health record of the clinic site. On average, women completed the iNEST pregnancy outcomes questionnaire 1.3 years after the end of the pregnancy (range 37 days to 3.0 years, n = 31 pregnancies among n = 30 women). In this substudy, the mean age upon completion of the first pregnancy questionnaire was 34.3 years; 82% (n = 22) of the women had completed 16 or more years of school. As shown in Supplementary Table SIII, there was extremely high correlation between the woman's self-report and the medical record for gestational age at birth or at miscarriage (Pearson correlation coefficient 0.995), and for birthweight (Pearson correlation coefficient 0.996).

Discussion

We enrolled 834 couples into a multicenter, multinational cohort study of subfertile couples, and followed them for up to 3 years. Enrollment was conducted at 10 different clinics across four different countries, with all clinics offering treatment for subfertility based on natural procreative technology. The mean woman's age (34.0 years) was similar to that of other treatment-based cohorts of subfertile couples (Luke *et al.*, 2012; McLernon *et al.*, 2016). Based on those with a reproductive history available, there were more participants with secondary infertility than primary infertility, while at least a third had a known prior history of other fertility treatment. In a substudy with medical records for one of the clinics, we documented high accuracy of patient-reported pregnancy outcomes. We also found that patient response rates for follow-up questionnaires were approximately double with reimbursement for both men and women (from 33–38% without reimbursement to 67–69% with reimbursement), except for pregnancy outcome questionnaires, which had similar response rates (74–78%), regardless of reimbursement.

Study duration

We were able to maintain the study for 10 years, after which the lack of ongoing funding made further maintenance not feasible.

Available data

Although the goal of the study protocol was to screen all potentially eligible patients, the proportion of screened couples who were eligible was reported to be 100% at some clinics, suggesting that screening may have been selective, or reported only for those who were eligible. Similarly, consent rates among eligible patients varied from 32% to 100%, with the higher consent rates again suggesting that the implementation and/or reporting of the screening and consenting process may not have been comprehensive at several of the clinics. In addition, we were not able to obtain demographic data for 36–43% of couples, or reproductive history for 17–24% of couples. The entrance questionnaire was completed by 58% of women, and about 59% had any follow-up questionnaire directly filled out by the woman or man. We received diagnostic data from the clinics for 77% of couples (643/834). We had more complete data for pregnancy outcomes (from clinics or participants), and female pelvic surgeries (from the clinics).

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Table III Female reproductive and treatment history, by clinical site (iNEST 2006–2016).

	Canada	Poland	UK	USA/LA	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All
	148	93	186	21	51	18	10	172	111	24	834
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Time trying to conceive (years)											
<1	49 (33.1)	0 (0.0)	11 (5.9)	2 (9.5)	6 (11.8)	2 (11.1)	0 (0.0)	32 (18.6)	22 (19.8)	4 (16.7)	128 (15.3)
1 to <3	50 (33.8)	6 (6.5)	60 (32.3)	6 (28.6)	19 (37.3)	9 (50.0)	1 (10.0)	82 (47.7)	41 (36.9)	9 (37.5)	283 (33.9)
3+	35 (23.7)	7 (7.5)	53 (28.5)	7 (33.3)	16 (31.4)	5 (27.8)	1 (10.0)	46 (26.7)	46 (41.4)	6 (25.0)	222 (26.6)
Missing	14 (9.5)	80 (86.0)	62 (33.3)	6 (28.6)	10 (19.6)	2 (11.1)	8 (80.0)	12 (7.0)	2 (1.8)	5 (20.8)	201 (24.1)
Prior pregnancy											
Yes	94 (63.5)	3 (3.2)	84 (45.2)	6 (28.6)	18 (35.3)	10 (55.6)	1 (10.0)	102 (59.3)	58 (52.3)	10 (41.7)	386 (46.3)
No	51 (34.5)	10 (10.8)	54 (29.0)	8 (38.1)	24 (47.1)	6 (33.3)	1 (10.0)	61 (35.5)	50 (45.0)	8 (33.3)	273 (32.7)
Missing	3 (2.0)	80 (86.0)	48 (25.8)	7 (33.3)	9 (17.7)	2 (11.1)	8 (80.0)	9 (5.2)	3 (2.7)	6 (25.0)	175 (21.0)
Prior live birth[a]											
Yes	22 (23.4)	1 (33.3)	54 (64.3)	4 (66.7)	11 (61.1)	8 (80.0)	1 (100.0)	65 (63.7)	26 (44.8)	7 (70.0)	199 (51.6)
No	27 (28.7)	2 (66.7)	30 (35.7)	2 (33.3)	7 (38.9)	1 (10.0)	0 (0.0)	33 (32.4)	17 (29.3)	2 (20.0)	121 (31.3)
Missing	45 (47.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	4 (3.9)	15 (25.9)	1 (10.0)	66 (17.1)
Prior ovulation drugs											
Yes	58 (39.2)	5 (5.4)	29 (15.6)	9 (42.9)	33 (64.7)	13 (72.2)	1 (10.0)	91 (52.9)	50 (45.0)	8 (33.3)	297 (35.6)
No	82 (55.4)	4 (4.3)	21 (11.3)	4 (19.0)	7 (13.7)	3 (16.7)	1 (10.0)	68 (39.5)	60 (54.1)	10 (41.7)	260 (31.2)
Missing	8 (5.4)	84 (90.3)	136 (73.1)	8 (38.1)	11 (21.6)	2 (11.1)	8 (80.0)	13 (7.6)	1 (0.9)	6 (25.0)	277 (33.2)
Prior IVF/ICSI											
Yes	9 (6.1)	1 (1.1)	23 (12.4)	1 (4.8)	2 (3.9)	0 (0.0)	0 (0.0)	15 (8.7)	5 (4.5)	0 (0.0)	56 (6.7)
No	132 (89.2)	12 (12.9)	73 (39.3)	12 (57.1)	37 (72.5)	16 (88.9)	2 (20.0)	76 (44.2)	104 (93.7)	18 (75.0)	482 (57.8)
Missing	7 (4.7)	80 (86.0)	90 (48.4)	8 (38.1)	12 (23.5)	2 (11.1)	8 (80.0)	81 (47.1)	2 (1.8)	6 (25.0)	296 (35.5)
Prior IUI											
Yes	17 (11.5)	4 (4.3)	34 (18.3)	1 (4.8)	4 (7.8)	1 (5.6)	0 (0.0)	41 (23.8)	21 (18.9)	0 (0.0)	123 (14.7)
No	125 (84.5)	5 (5.4)	88 (47.3)	12 (57.1)	36 (70.6)	15 (83.3)	2 (20.0)	116 (67.4)	89 (80.2)	18 (75.0)	506 (60.7)
Missing	6 (4.1)	84 (90.3)	64 (34.4)	8 (38.1)	11 (21.6)	2 (11.1)	8 (80.0)	15 (8.7)	1 (0.9)	6 (25.0)	205 (24.6)
Prior laparoscopy[b]											
Yes	15 (10.1)	0 (0.0)	17 (9.1)	3 (14.3)	15 (29.4)	5 (27.8)	0 (0.0)	38 (22.1)	15 (13.5)	4 (16.7)	112 (13.4)
No	78 (52.7)	0 (0.0)	32 (17.2)	10 (47.6)	25 (49.0)	10 (55.6)	2 (20.0)	118 (68.6)	74 (66.7)	13 (54.2)	362 (43.4)
Missing	55 (37.2)	93 (100.0)	137 (73.7)	8 (38.1)	11 (21.6)	3 (16.7)	8 (80.0)	16 (9.3)	22 (19.8)	7 (29.2)	360 (43.2)
Prior other pelvic surgery[c]											
Yes	15 (10.1)	0 (0.0)	17 (9.1)	5 (23.8)	14 (27.5)	6 (33.3)	1 (10.0)	47 (27.3)	19 (17.1)	4 (16.7)	128 (15.3)
No	78 (52.7)	0 (0.0)	32 (17.2)	8 (38.1)	26 (51.0)	9 (50.0)	1 (10.0)	110 (64.0)	69 (62.2)	13 (54.2)	346 (41.5)
Missing	55 (37.2)	93 (100.0)	137 (73.7)	8 (38.1)	11 (21.6)	3 (16.7)	8 (80.0)	15 (8.7)	23 (20.7)	7 (29.2)	360 (43.2)

LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia; iNEST: international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.

[a]Percentages are for those who had a prior pregnancy (n = 371).

[b]Includes laser, drill and laparoscopy procedures.

[c]Includes laparotomy, cystectomy, myomectomy, polypectomy, tubal and pelvic procedures.

Clinical site challenges

The limited funding of the study required that most of the study responsibilities at each study clinical site were carried out without compensation to the sites. This was the first research experience for the majority of the participating clinical sites, and most had difficulty designating time and structures for sufficient staff to perform the research functions of screening, obtaining informed consent, obtaining the entrance questionnaires and entering follow-up data for clinic visits, diagnoses, procedures and pregnancies. In a few clinical sites, all the study tasks were performed by the clinicians, without staff support: this was not a sustainable approach over time. Qualitatively, all clinical sites had difficulty developing practical procedures that could be consistently applied to invite eligible patients and obtain informed consent. One strategy that was felt to be successful in several clinics was to email information about the study and the consent to the patients

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prior to the first clinic visit. Some clinical sites assigned the function of obtaining informed consent to staff, but in most sites, the informed consent was obtained by the practicing physician or clinician, usually within the first two clinical visits. Some clinics incorporated the iNEST study entrance questionnaires into their clinical procedures as their own initial clinical questionnaires, which facilitated obtaining the baseline demographic and reproductive data. All clinics had a proportion of patients that were lost to follow-up from treatment. The clinical site in Lublin, Poland had additional challenges to translate all study instruments into Polish, and in setting up a separate server for data. An accident with the Polish server led to some data loss for their diagnoses and follow-up questionnaires. The clinical site in the UK had a number of patients whose first language was not English, which impaired completion of the study questionnaires.

Couple-based follow-up

We chose to conduct follow-up for this study based on both clinical data abstraction and direct contact with the couples, whether or not they continued with treatment at the participating clinic. Therefore, we retained couples in the study who at some point decided to go to a different clinic for fertility treatment or who decided to not continue any treatment. This gives an opportunity for insight into patterns of continuing with treatment, as well as a broader range of treatments received. We endeavored to have follow-up on patients dropping out of the clinic treatment. However, there was a lower level of response to follow-up questionnaires than we hoped, which limits the ability to obtain complete data on patterns of treatment continuation or switching. Most clinic-based fertility studies have discontinuation rates from treatment of 30% or more, up to 60%, for a variety of reasons, and ours is not out of range in this regard (Gameiro *et al.*, 2012). Our finding of differential follow-up by whether patients are reimbursed or not for their questionnaires is also not surprising. Other researchers have found similarly that offering participants trying to conceive incentives after enrollment can boost cohort retention (Wise *et al.*, 2020). This provides important perspective for future studies that attempt to follow couples apart from their clinic visits, particularly for outcomes

Table IV Available data by clinical site (iNEST 2006–2016).

	Canada	Poland	UK	USA/LA	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All
	148	93	186	21	51	18	10	172	111	24	834
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Woman's Entrance Questionnaire	94 (63.5)	10 (10.8)	45 (24.2)	13 (61.9)	41 (80.4)	15 (83.3)	2 (20.0)	158 (91.9)	89 (80.2)	17 (70.8)	484 (58.0)
Man's Entrance Questionnaire	69 (46.6)	0 (0.0)	45 (24.2)	14 (66.7)	28 (54.9)	11 (61.1)	1 (10.0)	143 (83.1)	81 (73.0)	8 (33.3)	400 (48.0)
Follow-up Questionnaire (woman or man)	124 (83.8)	0 (0.0)	51 (27.4)	21 (100.0)	42 (82.4)	15 (83.3)	7 (70.0)	135 (78.5)	83 (74.8)	17 (70.8)	495 (59.4)
Woman's Creighton Model Chart	106 (71.6)	2 (2.2)	0 (0.0)	15 (71.4)	40 (78.4)	16 (88.9)	0 (0.0)	89 (51.7)	72 (64.9)	12 (50.0)	352 (42.2)
Clinic visits	131 (88.5)	9 (9.7)	83 (44.6)	0 (0.0)	47 (92.2)	18 (100.0)	0 (0.0)	158 (91.9)	110 (99.1)	20 (83.3)	496 (59.5)
Diagnoses	123 (83.1)	90 (96.8)	83 (44.6)	0 (0.0)	48 (94.1)	18 (100.0)	10 (100.0)	172 (100.0)	79 (71.2)	20 (83.3)	643 (77.1)
Medications	80 (54.1)	0 (0.0)	82 (44.0)	13 (61.9)	42 (82.3)	10 (55.6)	1 (10.0)	90 (52.3)	69 (62.2)	4 (16.7)	391 (46.9)

LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia ;iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.

Table V Pregnancies and live births during study, by clinical site (iNEST 2006–2016).

	Canada	Poland	UK	USA/LA	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All
	148	93	186	21	51	18	10	172	111	24	834
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any pregnancy	110 (74.3)	35 (37.6)	69 (37.1)	14 (66.7)	31 (60.8)	14 (77.8)	4 (40.0)	106 (61.6)	73 (65.8)	17 (70.8)	473 (56.7)
Any live birth	96 (64.9)	25 (26.9)	53 (28.5)	8 (38.1)	26 (51.0)	10 (55.6)	4 (40.0)	79 (45.9)	55 (49.5)	13 (54.2)	369 (44.2)

LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia; iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.
Percentages are expressed as proportion of all couples at site.

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Table VI Clinical diagnoses, by clinical site (iNEST 2006–2016).

	Canada	Poland	UK	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All[a]
	123	90	83	48	18	10	172	79	20	643
FEMALE										
Metabolic conditions	45 (36.6)	22 (24.4)	23 (27.7)	17 (35.4)	3 (16.7)	2 (20.0)	61 (35.5)	36 (45.6)	4 (20.0)	213 (33.1)
PCOS	29 (23.6)	10 (11.1)	9 (10.8)	10 (20.8)	3 (16.7)	2 (20.0)	54 (31.4)	30 (38.0)	4 (20.0)	151 (23.5)
Elevated androgens	5 (4.1)	5 (5.6)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	13 (7.6)	0 (0.0)	0 (0.0)	24 (3.7)
Overweight and obesity	6 (4.9)	1 (1.1)	17 (20.5)	4 (8.3)	0 (0.0)	0 (0.0)	17 (9.9)	10 (12.7)	0 (0.0)	55 (8.6)
Insulin resistance	19 (15.5)	13 (14.4)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	34 (19.8)	2 (2.5)	1 (5.0)	70 (10.9)
Underweight	0 (0.0)	0 (0.0)	0 (0.0)	5 (10.4)	0 (0.0)	0 (0.0)	2 (1.2)	3 (3.8)	0 (0.0)	10 (1.6)
Ovulation-related disorders	118 (95.9)	60 (66.7)	78 (94.0)	43 (89.6)	18 (100.0)	0 (0.0)	165 (95.9)	60 (76.0)	14 (70.0)	556 (86.5)
Anovulation or oligoovulation	39 (31.7)	18 (20.0)	4 (4.8)	2 (4.2)	3 (16.7)	0 (0.0)	21 (12.2)	18 (22.8)	0 (0.0)	105 (16.3)
Ultrasound disorders of follicular development	15 (12.2)	11 (12.2)	65 (78.3)	3 (6.3)	5 (27.8)	0 (0.0)	66 (38.4)	5 (6.3)	2 (10.0)	172 (26.8)
Low follicular estradiol levels	54 (43.9)	4 (4.4)	11 (13.3)	29 (60.4)	4 (22.2)	0 (0.0)	93 (54.1)	2 (2.5)	2 (10.0)	199 (31.0)
Luteal phase insufficiency [b]	108 (87.8)	43 (47.8)	73 (88.0)	38 (79.2)	18 (100.0)	0 (0.0)	162 (94.2)	41 (51.9)	14 (70.0)	497 (77.3)
Reduced ovarian reserve	7 (5.7)	5 (5.6)	13 (15.7)	1 (2.1)	2 (11.1)	0 (0.0)	32 (18.6)	7 (8.9)	0 (0.0)	67 (10.4)
Thyroid disorders	30 (24.4)	31 (34.4)	9 (10.8)	8 (16.7)	0 (0.0)	1 (10.0)	85 (49.4)	11 (13.9)	10 (50.0)	185 (28.8)
Hyperprolactinemia	6 (4.9)	71 (78.9)	0 (0.0)	3 (6.3)	0 (0.0)	0 (0.0)	5 (2.9)	3 (3.8)	0 (0.0)	88 (13.7)
Endometriosis	14 (11.4)	30 (33.3)	20 (24.1)	37 (77.1)	7 (38.9)	0 (0.0)	64 (37.2)	25 (31.7)	5 (25.0)	202 (31.4)
Pelvic adhesions	2 (1.6)	16 (17.8)	15 (18.1)	11 (22.9)	3 (16.7)	0 (0.0)	17 (9.9)	5 (6.3)	3 (15.0)	72 (11.20)
Uterine factors	16 (13.0)	16 (17.8)	8 (9.6)	6 (12.5)	1 (5.6)	1 (10.0)	39 (22.7)	16 (20.3)	5 (25.0)	108 (16.8)
Fibroids	4 (3.3)	10 (11.1)	5 (6.0)	4 (8.3)	1 (5.6)	1 (10.0)	28 (16.3)	6 (7.6)	4 (20.0)	63 (9.8)
Polyps	9 (7.3)	7 (7.8)	4 (4.8)	3 (6.3)	0 (0.0)	0 (0.0)	14 (8.1)	6 (7.6)	0 (0.0)	43 (6.7)
Müllerian anomalies	3 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.3)	3 (3.8)	1 (5.0)	11 (1.7)
Tubal factor/blockage	7 (5.7)	11 (12.2)	10 (12.1)	7 (14.6)	2 (11.1)	0 (0.0)	37 (21.5)	10 (12.7)	1 (5.0)	85 (13.2)
Infections	29 (23.6)	3 (3.3)	2 (2.4)	6 (12.5)	0 (0.0)	0 (0.0)	28 (16.3)	33 (41.8)	3 (15.0)	104 (16.2)
Chronic endometritis	8 (6.5)	2 (2.2)	2 (2.4)	6 (12.5)	0 (0.0)	0 (0.0)	22 (12.8)	32 (40.5)	2 (10.0)	74 (11.5)
Other female urogenital infection	24 (19.5)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.5)	1 (1.3)	1 (5.0)	33 (5.1)
Immune disorders	9 (7.3)	16 (17.8)	1 (1.2)	1 (2.1)	1 (5.6)	0 (0.0)	14 (8.1)	2 (2.5)	0 (0.0)	44 (6.8)
Nutritional disorders	94 (76.4)	68 (75.6)	20 (24.1)	18 (37.5)	2 (11.1)	0 (0.0)	81 (47.1)	19 (24.1)	1 (5.0)	303 (47.1)
Vitamin D deficiency	46 (37.4)	57 (63.3)	1 (1.2)	14 (29.2)	1 (5.6)	0 (0.0)	80 (46.5)	17 (21.5)	0 (0.0)	216 (33.6)
Vitamin B12 deficiency	25 (20.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.8)	0 (0.0)	0 (0.0)	35 (5.4)
Iron deficiency	55 (44.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	56 (8.7)
Food intolerance/allergy	20 (16.3)	53 (58.9)	20 (24.1)	0 (0.0)	1 (5.6)	0 (0.0)	5 (2.9)	2 (2.5)	1 (5.0)	102 (15.9)
Mental health diagnoses	10 (8.3)	0 (0.0)	1 (1.2)	5 (10.4)	0 (0.0)	0 (0.0)	32 (18.6)	3 (3.8)	0 (0.0)	51 (7.9)
Other female diagnoses	27 (22.0)	8 (8.9)	3 (3.6)	21 (43.8)	6 (33.3)	1 (10.0)	26 (15.1)	22 (27.9)	6 (30.0)	120 (18.66)
FEMALE SYMPTOMS										
Premenstrual syndrome	56 (45.5)	6 (6.7)	63 (75.9)	31 (64.6)	9 (50.0)	0 (0.0)	52 (30.2)	44 (55.7)	6 (30.0)	267 (41.5)
Abnormal uterine bleeding	0 (0.0)	0 (0.0)	0 (0.0)	19 (39.6)	0 (0.0)	1 (10.0)	1 (0.6)	16 (20.3)	0 (0.0)	37 (5.8)
Reduced cervical mucus	62 (50.4)	46 (51.1)	54 (65.1)	32 (66.7)	15 (83.3)	0 (0.0)	106 (61.6)	40 (50.6)	0 (0.0)	355 (55.2)
Clinical endorphin deficiency	21 (17.1)	2 (2.2)	47 (56.6)	20 (41.7)	3 (16.7)	0 (0.0)	36 (20.9)	0 (0.0)	0 (0.0)	129 (20.1)
MALE										
Semen analysis abnormalities	13 (10.6)	38 (42.2)	38 (45.8)	9 (18.8)	4 (22.2)	0 (0.0)	18 (10.5)	27 (34.2)	4 (20.0)	151 (23.5)
Low count	7 (5.7)	17 (18.9)	11 (13.3)	5 (10.4)	3 (16.7)	0 (0.0)	13 (7.6)	8 (10.1)	0 (0.0)	64 (10.0)
Low motility	10 (8.1)	14 (15.6)	22 (26.5)	5 (10.4)	2 (11.1)	0 (0.0)	6 (3.5)	12 (15.9)	2 (10.0)	73 (11.4)
Poor morphology	3 (2.4)	34 (37.8)	23 (27.7)	6 (12.5)	4 (22.2)	0 (0.0)	5 (2.9)	21 (26.6)	3 (15.0)	99 (15.4)
Varicocele	4 (3.3)	10 (11.1)	5 (6.0)	1 (2.1)	1 (5.6)	0 (0.0)	2 (1.2)	4 (5.1)	0 (0.0)	27 (4.2)
Endocrine disorders	0 (0.0)	8 (8.9)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	4 (2.3)	2 (2.5)	0 (0.0)	15 (2.3)
Other male diagnoses	3 (2.4)	11 (12.2)	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)	2 (1.2)	5 (6.3)	0 (0.0)	23 (3.6)
COUPLE										
Unexplained infertility	3 (2.4)	8 (8.9)	11 (13.3)	0 (0.0)	1 (5.6)	1 (10.0)	0 (0.0)	0 (0.0)	1 (5.0)	25 (3.9)

MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia; PCOS, polycystic ovary syndrome; iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.

[a]Percentages will not sum to 100% because most participants had more than one diagnosis. The mean number of diagnoses per couple was 4.7 excluding female symptoms, and 6.0 including female symptoms.

[b]Luteal insufficiency was identified by short luteal phase or by low progesterone and/or estradiol levels measured serially during the luteal phase.

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Table VII Medications taken, by clinical site (iNEST 2006–2016).[a]

	Canada	UK	USA/LA	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All
	80	82	13	42	10	1	90	69	4	391
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General health										
Folic acid	34 (42.5)	3 (3.7)	9 (69.2)	17 (40.5)	2 (20.0)	1 (100.0)	45 (50.0)	24 (34.8)	0 (0.0)	135 (34.5)
Multi/prenatal vitamin	50 (62.5)	2 (2.4)	11 (84.6)	20 (47.6)	3 (30.0)	1 (100.0)	59 (65.6)	41 (59.4)	0 (0.0)	187 (47.8)
Glucose metabolism										
Metformin	21 (26.3)	3 (3.7)	6 (46.2)	10 (23.8)	1 (10.0)	0 (0.0)	12 (13.3)	15 (21.7)	1 (25.0)	69 (17.6)
Pioglitazone	0 (0.0)	0 (0.0)	1 (7.7)	2 (4.8)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.4)	0 (0.0)	5 (1.3)
Glyburide	0 (0.0)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	0 (0.0)	3 (0.8)
Cervical mucus enhancement										
Vitamin B6	30 (37.5)	1 (1.2)	10 (76.9)	16 (38.1)	1 (10.0)	1 (100.0)	50 (55.6)	18 (26.1)	0 (0.0)	127 (32.5)
Guaifenesin	20 (25.0)	0 (0.0)	9 (69.2)	19 (45.2)	3 (30.0)	0 (0.0)	46 (51.1)	10 (14.5)	0 (0.0)	107 (27.4)
Other medications for cervical mucus[b]	2 (2.5)	22 (26.8)	3 (23.1)	2 (4.8)	0 (0.0)	0 (0.0)	9 (10.0)	4 (5.8)	0 (0.0)	42 (10.7)
Ovulation stimulation										
Clomiphene citrate	33 (41.3)	54 (65.9)	3 (23.1)	8 (19.0)	1 (10.0)	0 (0.0)	31 (34.4)	19 (27.5)	1 (25.0)	150 (38.4)
Letrozole	26 (32.5)	35 (42.7)	6 (46.2)	25 (59.5)	2 (20.0)	0 (0.0)	22 (24.4)	8 (11.6)	0 (0.0)	124 (31.7)
Other oral ovulation medication[c]	4 (5.0)	0 (0.0)	1 (7.7)	2 (4.8)	0 (0.0)	0 (0.0)	9 (10.0)	8 (11.6)	0 (0.0)	24 (6.1)
Injectable ovulation medication	1 (1.3)	1 (1.2)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	12 (13.3)	5 (7.2)	0 (0.0)	20 (5.1)
HCG, trigger injection	5 (6.3)	38 (46.3)	2 (15.4)	3 (7.1)	0 (0.0)	0 (0.0)	6 (6.7)	9 (13.0)	1 (25.0)	64 (16.4)
Luteal phase support										
HCG, multiple injections	12 (15.0)	66 (80.5)	11 (84.6)	9 (21.4)	1 (10.0)	0 (0.0)	30 (33.3)	18 (26.1)	0 (0.0)	147 (37.6)
Progesterone	71 (88.8)	24 (29.3)	8 (61.5)	32 (76.2)	6 (60.0)	0 (0.0)	53 (58.9)	39 (56.5)	3 (75.0)	236 (60.4)
Other hormones										
Thyroid replacement	11 (13.8)	5 (6.1)	6 (46.2)	6 (14.3)	1 (10.0)	0 (0.0)	33 (36.7)	4 (5.8)	1 (25.0)	67 (17.1)
Corticosteroid	3 (3.8)	0 (0.0)	1 (7.7)	8 (19.0)	0 (0.0)	0 (0.0)	4 (4.4)	4 (5.8)	0 (0.0)	20 (5.1)
Estrogen	3 (3.8)	0 (0.0)	5 (38.5)	2 (4.8)	0 (0.0)	0 (0.0)	5 (5.6)	0 (0.0)	1 (25.0)	16 (4.1)
Other										
Any antibiotic	19 (23.8)	1 (1.2)	5 (38.5)	16 (38.1)	2 (20.0)	0 (0.0)	39 (43.3)	14 (20.3)	0 (0.0)	96 (24.6)
Naltrexone (low dose)	22 (27.5)	25 (30.5)	6 (46.2)	10 (23.8)	2 (20.0)	0 (0.0)	24 (26.7)	9 (13.0)	1 (25.0)	99 (25.3)
Bromocriptine	1 (1.3)	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	4 (1.0)
Aspirin (low dose)	4 (5.0)	1 (1.2)	1 (7.7)	3 (7.1)	1 (10.0)	0 (0.0)	12 (13.3)	10 (14.5)	0 (0.0)	32 (8.2)

LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia; iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.

[a]Percentages of all women at each site with medication data; obtained by medical record abstraction in UK; obtained from patient follow-up questionnaires for all other sites. Percentages do not sum to 100% because women could take more than one medication.

[b]Includes 'Fertile CM' herbal mixture supplement, and unknown preparations for mucus enhancement.

[c]Includes vitex (chasteberry), anastrozole, herbal mixture supplements and unknown preparations for ovulation.

other than pregnancy or live birth. At the same time, our data provided encouragement from one of our sites in that when patients do report on pregnancy outcomes, they do so accurately.

Value of cohort data

Subfertile couples and the clinicians advising them require good cohort data (not just per-cycle data) to understand treatment outcomes and prognostic factors impacting those outcomes (Luke *et al.*, 2012; McLernon *et al.*, 2016). Multicenter clinic-based studies contribute data that can overcome the limitations related to specific population factors in single-clinic studies, which may be unmeasured, and which can also provide clues for the impact of practice variation on outcomes (Diamond *et al.*, 2019). The most comprehensive multicenter studies for subfertility are the large national or regional registries for ART, which have contributed greatly to the understanding and development of ART practice (Zegers-Hochschild *et al.*, 2015; Chambers *et al.*, 2016, 2017; Sunderam, 2020). Recently, there has been increasing recognition of the need for registries for subfertility treatment other than ART (Spandorfer, 2020; Stanford *et al.*, 2020a).

However, a large proportion of couples with subfertility do not obtain treatment through conventional medicine clinics, or combine different treatments, or may switch between clinics (Smith *et al.*, 2010; Stanford *et al.*, 2016; Righarts *et al.*, 2017). Therefore, studies that follow couples directly, independently of a specific system of clinics,

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Table VIII Female pelvic procedures during study, by clinical site (iNEST 2006–2016).

	Canada	Poland	UK	USA/LA	USA/MA	USA/MO	USA/NC	USA/NJ	USA/UT	USA/VA	All
	148	93	186	21	51	18	10	172	111	24	834
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any pelvic procedure[a]	26 (17.6)	33 (35.5)	23 (12.4)	0 (0.0)	29 (56.9)	9 (50.0)	4 (40.0)	8 (4.7)	45 (40.5)	6 (25.0)	183 (21.9)
Laparoscopy[b]	22 (84.6)	24 (72.7)	20 (87.0)	0 (0.0)	29 (100.0)	6 (66.7)	1 (25.0)	8 (100.0)	33 (73.3)	6 (100.0)	149 (81.4)
Laparotomy[b]	1 (3.8)	2 (6.1)	1 (4.3)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	6 (3.3)
Robotic assisted[b]	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (11.1)	4 (100.0)	0 (0.0)	0 (0.0)	4 (66.7)	11 (6.0)
Hysteroscopy[b]	14 (53.8)	10 (30.3)	4 (17.4)	0 (0.0)	28 (96.6	6 (66.7)	0 (0.0)	5 (62.5)	12 (26.7)	6 (100.0)	85 (46.4)
Selective hysterosalpingography[b]	4 (15.4)	3 (9.1)	3 (13.0)	0 (0.0)	9 (31.0)	6 (66.7)	0 (0.0)	8 (100.0)	4 (8.9)	6 (100.0)	43 (23.5)
Hysterosalpingogram[b]	19 (73.1)	12 (36.4)	4 (17.4)	0 (0.0)	27 (93.1)	8 (88.9)	0 (0.0)	8 (100.0)	31 (68.9)	5 (83.3)	114 (62.3)
Chromopertubation[b]	0 (0.0)	19 (57.6)	8 (34.8)	0 (0.0)	15 (51.7)	0 (0.0)	0 (0.0)	0 (0.0)	11 (24.4)	0 (0.0)	53 (29.0)

LA, Louisiana; MA, Massachusetts; MO, Missouri; NC, North Carolina; NJ, New Jersey; UT, Utah; VA, Virginia; iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.
[a]Percentages of all women at each site with any pelvic procedure.
[b]Percentages of all women who had any procedure per site. Column percentages will not sum to 100% because some patients had more than one procedure.

Table IX Response to follow-up and pregnancy questionnaires by time frame and compensation status (iNEST 2006–2016).

Questionnaire type	Time period and compensation status	Number sent[a]	Number returned completed
			n (%)
Women's yearly follow-up	February 2014 to February 2015, compensated[b]	42	29 (69.0)
	February 2015 to February 2016, not compensated	47	18 (38.3)
Men's yearly follow-up	February 2014 to February 2015, compensated[b]	42	28 (66.7)
	February 2015 to February 2016, not compensated	40	13 (32.5)
Pregnancy questionnaire	February 2014 to February 2015, compensated[b]	101	79 (78.2)
	February 2015 to February 2016, not compensated	47	35 (74.5)

[a]Excludes incorrect email addresses.
[b]Participants received $20 gift card after completing the questionnaire.
iNEST, international Natural Procreative Technology Evaluation and Surveillance of Treatment for Subfertility.

provide important additional information about the long-term prognosis for pregnancy, both treatment-related and treatment-independent (Malchau *et al.*, 2017). National cohorts can provide important data linking, but still have limitations related to the data available from medical systems and vital registries. With the iNEST study protocol, we sought to conduct a hybrid study that would include all couples starting at multiple participating clinical sites and continue prospective follow-up regardless of whether they continued treatment with that clinical site, or any clinical site. While modest funding was available to compensate participants for active follow-up we had reasonable response rates, but once funding was no longer available the response rate to follow-up was not acceptable.

Strengths

This is the first multicenter study of clinics employing natural procreative technology, a comprehensive restorative reproductive medicine approach for subfertility. Data from the iNEST cohort will yield insight into prognostic factors, and perhaps practice factors (based on natural variability between different clinical sites) influencing pregnancy and live birth outcomes. We also will look for factors influencing discontinuation of treatment, and satisfaction.

Limitations

The level of missing data was higher than anticipated for some descriptive and prognostic variables, particularly time trying to conceive (24% overall; range between sites 2–86%), prior pregnancy history (21% overall; range between sites 3–86%) and prior fertility treatments (25–36% overall; range between sites 1–90%), as well as diagnoses, CrM charts and medications, which limits both generalizability and the ability to study different components of treatment and prognosis. When missing data are differential with respect to exposure and outcome, it can also threaten internal validity (Stanford *et al.*, 2016). However, our

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main outcome data (pregnancy and live birth) are robust, which may somewhat mitigate this concern. Most of the participating clinicians were not surgeons, which limits the opportunity to study the impact of surgical interventions. Participants were geographically dispersed but relatively homogeneous with regard to socioeconomic status, which may limit the generalizability of current and future findings. It is possible that couples who discontinue treatment may have a less favorable prognosis than those couples who continue (Stolwijk *et al.*, 2000).

Future analyses from the iNEST cohort

For future analyses, we will examine pregnancy rates and live birth rates, with appropriate adjustments by survival analysis for drop out from treatment, and stratifications or adjustments for prognostic variables: woman's age, prior pregnancy history (prior pregnancy yes/no, prior birth yes/no), time trying (e.g. those trying for less than a year, 1–3 years, and those trying for >3 years), prior treatment history (prior attempts with ovulation drugs, and/or IU and/or ART). This will be analyzed using standard lifetable techniques to deal with censored data (i.e. couples for whom treatment and pregnancy status cannot be ascertained beyond a certain time period). The primary analysis will include all treatment without time-varying factors other than initiation and discontinuation of treatment. We will compare couples who receive natural procreative technology, with those who have follow-up data but ceased to receive treatment. For the purposes of this study, ceasing to receive treatment is defined as not receiving any components of natural procreative technology, as reported in patient questionnaires and/or clinical records. This will be operationalized in 3-month time intervals. For patient-reported treatment data from questionnaires, the time point of ceasing treatment may be estimated by gaps between the questionnaires. Cox proportional hazards regression will be used in an exploratory manner to investigate demographic and reproductive characteristics (particularly woman's age, prior pregnancy and time trying to conceive) that may be associated with a greater likelihood of successful live birth. By stratification, we will also explore the impact of specific diagnoses and specific interventions (treatment components) for live birth, possibly with time-varying indicators, to the extent that data allows. In addition, we will be able to explore demographic and reproductive factors that are associated with continuation of treatment and cohort retention.

For missing covariate data that is not >25% missing, we will use multiple imputation techniques for data completion. As a sensitivity analysis, we will also consider missing values as a separate response category. We will conduct case-wise removal of sites to assess for site heterogeneity. (One site has a high level of missing data and will need to be removed from many analyses.) We will test statistically for site effects and where these are found we will control for site in the survival analyses. An analogous set of analyses will be repeated for the secondary outcome of conception (clinical pregnancy), without reference to pregnancy outcome.

There is a possibility for bias from differential drop out in relation to prognosis. We will address this in two ways. The first is a sensitivity analysis, wherein all couples who exit will be analyzed as if continuing for the follow-up duration with no pregnancy (i.e. the most conservative estimate; Stolwijk *et al.*, 2000). Second, we will consider demographic factors that are predictive of continuation in treatment (versus dropout), and based on those factors, apply inverse probability weighting to adjust the results for those continuing in the study (Modest *et al.*, 2018).

Future research

For future research beyond this study, our experience with the iNEST protocol suggests two possible pathways. We believe both have value and should be pursued.

First, we believe our data support the viability of the approach to identify and follow couples prospectively for their fertility treatment and lifestyle choices, independently of clinics. Our data indicate the value of following up with men as well as women. Recruitment can occur through online outreach (Wise *et al.*, 2015) or through population-based approaches (Stanford *et al.*, 2016). This approach will likely require sufficient funding to compensate couples for their responses to questionnaires, particularly for more detailed questionnaires.

Second, we believe that streamlined registry-based protocols for patients receiving treatment approaches for subfertility other than ART need to be developed, despite the intrinsic limitations of sparse data on potential confounders that a registry poses (Ferraretti *et al.*, 2017). Because a registry will require much less intensive engagement of clinical staff, we believe it would be significantly more likely to be implemented by participating clinics. The success and contribution of ART-based registries highlight the possibilities for registries of other fertility treatments (Spandorfer, 2020; Stanford *et al.* 2020a). For the most meaningful results, such registries will need to be patient-based, rather than based on single cycles of treatment.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

Deidentified analytic data for this manuscript may be available upon request and approval of the responsible authorities at the University of Utah.

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Authors' roles

J.B.S., T.P. and K.K. designed the study and supervised its initial implementation. J.B.S. supervised all aspects of conducting the study and

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analysis and wrote the manuscript. M.R.R., S.N., K.J., I.M., H.H. and E.T. conducted the analysis. I.M. was also a data center coordinator. I.R. and K.G. contributed to study implementation, including regulatory structures and data collection systems, respectively. J.B.S., E.T., I.W., K. G., A.C., A.S., J.G.T., M.B., B.M., P.C., K.P., R.C., P.D. and L.L. contributed study data, including medical record abstraction. All authors critically reviewed and revised the final manuscript.

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Conflict of interest

The authors have no conflicts of interest to declare.

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