THE FERTILITY EXPERIENCES STUDY: THE COMPLEXITIES OF INFERTILITY RESEARCH, TREATMENT APPROACHES, AND OUTCOMES

by

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A dissertation submitted to the faculty of
The University of Utah
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

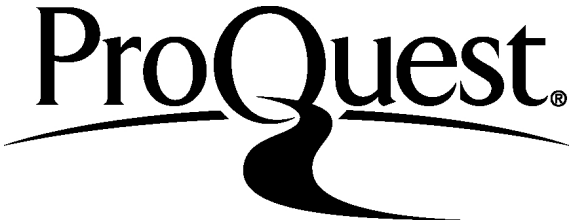
in

Public Health

Department of Family and Preventive Medicine

The University of Utah

May 2015



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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Infertility is traditionally defined as failure to achieve pregnancy after 12 or more months of regular unprotected intercourse; an estimated 10-15% of women experience infertility at some point in their reproductive life. The majority of infertility research has been focused on couples actively seeking treatment in specialty clinics, overlooking individuals who are infertile but not seeking medical specialty treatment. This dissertation uses data from the Fertility Experiences to examine the complexities of infertility research, treatment and interventions, and outcomes. Aim 1 compares approaches to collecting information about pregnancy attempt duration and identifies predictors of misestimating time at risk for pregnancy when assessing duration using a single question compared to discrete date event histories. Aim 2 provides information on the use of interventions to enhance fertility over the course of the reproductive life. Aim 3 examines the association between infertility treatment (ovulation stimulation, intrauterine insemination (IUI), and in-vitro fertilization (IVF)) used during the cycle of conception and preterm birth (<37 weeks completed gestation) using subfertile women who conceived spontaneously, without medical treatment, as controls.

Aim one found that two-thirds of women substantially misestimated their biological time at risk for pregnancy when asked a single question. Detailed attempt histories, capturing specific dates, can provide a more nuanced assessment of biological

time at risk of pregnancy, duration of intentional pregnancy attempt, and specifically the number of cycles where fertility focused intercourse is being used to ensure appropriately timed intercourse. Aim two found that women commonly use both medical and nonmedical interventions while trying to conceive. Primary care clinicians and fertility specialists should assume that nearly all their patients are using some type of nonmedical intervention and should take a full history that includes assessment of behavioral changes and complementary and alternative medicine. Aim three found that all fertility treatments (ovulation drugs, IUI, and IVF) were associated with a higher incidence of preterm birth, predominantly related to multiple gestation births. The findings support the use of treatment protocols that maximize singleton gestation. In addition, the findings highlight the increased risk of preterm birth in pregnancies conceived using any medical fertility treatment, not just IVF.

This work is dedicated to the women who have encountered challenges along their journey to achieve their reproductive desires and the practitioners who compassionately support them. This research would not have been possible without the women who shared stories. Thank you.

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ACKNOWLEDGEMENTS

I would like to thank my advisor, committee chair, and mentor, Dr. Joseph B Stanford, and my supervising committee members, Dr. Sara E Simonsen, Dr. Christina A. Porucznik, Dr. Kenneth Smith, and Dr. Ahmad Hammoud for the guidance, feedback, and support throughout this process. This work would not have been possible without the amazing FES research team, which included Scarlett Reeves, Mandy Ward, Stephanie Croasdell, Leslie McNaughtan, Alicia Fadrowsky, Melissa Sperry, Alessandra Zimmerman, Varsha Iyer, Erik Linn, Melody Anderson, Namea Sells, and Mohammed Al-Temimi. Other collaborators in the FES project include Dr. Mark Gibson, Dr. Shawn Gurtcheff, Dr. Marcia Feldkamp, Dr. Jaewhan Kim, Dr. James Heiner, Dr, Rita Sharshiner, Carra Christopher, Alision Frasier, and Jahn Barlow. This work was supported by grants from the Primary Children's Medical Center Foundation, Salt Lake City, Utah, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, R21 HD060213-01A1.

I would also like to thank my husband, Alexander Sanders, for his patience, encouragement, humor, and home cooked meals during the dissertation writing process. This would not have been possible without you. I look forward to the next chapter. I would also like to thank my parents, Michael and Marcia Nichols, for their support and reassurance through every step of my academic journey and being role models in the

pursuit of lifelong learning. A special thanks to the amazing women in my book-group/ski-troupe/mountain-biking/dog-hiking life who keep me feeling connected and continuously remind me to delight in the journey. And last but not least, I would like to thank the inspiring women in my Public Health PhD cohort.

CHAPTER 1

BACKGROUND AND INTRODUCTION

1.1 Overview of Subfertility

Subfertility, also called infertility, is traditionally defined as failure to achieve pregnancy after 12 or more months of regular unprotected intercourse. About 15% of women in the United States who are currently attempting to conceive are experiencing difficulty becoming pregnant.[1-3] About half of these women seek medical treatment, with significant disparities among socioeconomic and ethnic groups.[1,4,5] Subfertile couples and their clinicians choose among a variety of treatment options.[6,7]

1.2 Etiology and Management of Infertility in the United States

There are varying degrees of subfertility and a variety of potential underlying causes: abnormalities in oocyte production; abnormalities in sperm production; abnormalities in reproductive tract transport of the sperm, oocyte, and/or embryo; abnormalities in the implantation process; or other conditions that affect one or multiple components of the reproductive process.[8] Diagnostic tests, monitoring biosymptoms, and tracking menstrual cycle patterns can help to determine the underlying etiology of the unsuccessful pregnancy attempts.[9] However, providers are frequently unable to identify the precise cause of a couple's subfertility and in 15-30% of cases assign more

ambiguous diagnosis of unexplained infertility.[10] In the United States, about half of couples who have difficulty conceiving seek medical treatment to address their subfertility.[11] Common medical approaches to overcoming subfertility include the use of ovulation stimulation (OS), intrauterine insemination (IUI), and in vitro fertilization (IVF).

Women with ovulatory dysfunction are commonly treated with fertility drugs that stimulate ovulation.[12] Clomiphene citrate (CC), brand names Clomid® and Serophene®, is the most commonly used oral medication for ovulation indication. The general principle behind CC is that it acts on the pituitary gland to increase secretion of FSH, which in turn stimulates the maturation of ovarian follicles. In successful CC treatment, the pituitary gland becomes hypersensitive to gonadotropin-releasing hormone (GnRh), which causes a luteinizing hormone (LH) surge, which signals the release of an egg from the mature follicle during ovulation.

Intrauterine insemination (IUI) is most commonly used when male factor is a contributor to a couple's infertility. Couples in which the male has low sperm count or impaired sperm motility may benefit from this type of fertility treatment as it allows for semen to bypass the cervix.[13] IUI consists of collecting semen, then washing the ejaculate to remove prostaglandins and other factors. The sperm is then concentrated in a small volume of culture media that enhances capacitation and the acrosome reaction.[8] The mixture is then injected directly into the upper uterine cavity using a small catheter threaded through the upper cervix.[13] This procedure is timed just prior to ovulation. IUI success depends on the cause and severity of the couple's infertility. IUI is most beneficial for couples if the man has motility issues or the woman has cervical factor

infertility. IUI does not help couples in which the women suffer from tubal factor infertility, or severe endometriosis, or men have very low sperm count.[13]

IVF is used to increase the chances of conceiving in multiple underlying causes of infertility. It consists of various steps including ovarian stimulation, egg retrieval, fertilization, embryo culture, and embryo transfer.[14] With IVF, both the oocyte and the sperm are handled outside of the body. Semen is collected from the male partner and either placed in the petri dish with the egg overnight or a single sperm is injected directly into each mature egg, a procedure known as intracytoplasmic sperm injection (ICSI). ICSI is used in about 60% of assisted reproductive technology (ART) cycles in the United States.[14]

In the past 3 decades, the focus of fertility research and treatment has increasingly shifted from less invasive medical treatments (including OS and IUI) to the more invasive IVF. IVF was originally developed to overcome absolute subfertility due to blockage or absence of the fallopian tubes and later expanded to treat severe male subfertility with the addition of intracytoplasmic sperm injection (ICSI) (i.e., specific indications for IVF), but is now frequently used for couples with diminished fertility due to any cause as well as those with infertility of unknown cause.[15,16] While providers advocate that IVF should become a primary management strategy for couples without specific indications because of its high probability of per cycle success, there are substantial concerns about expanding use of IVF, including high cost and impact on neonatal outcomes.[15,16] The proportion of live births conceived through IVF average 1.4% in the United States but vary by region (range: 0.2% in Puerto Rico to 4.3% in Massachusetts)[17]; however, across the nation IVF births contribute to a considerable

proportion of the preterm births (PTB, <37 weeks completed gestation) and low birthweight (LBW, <2,500 grams) infants born each year. No formal surveillance exists for the less invasive fertility treatments, but exposure to these fertility treatments (OS and IUI) may also be associated with adverse perinatal outcomes.[18-20] It is estimated that OS accounts for up to 6% of the births in the United States, and about 1% of births results from IUI.[7,18] Therefore, monitoring birth outcomes and assessing risks associated with each of these medical exposures are critical public health concerns. Additional questions remain as to whether PTB and LBW are related to the treatments or to the underlying causes or severity of the subfertility.[21,22] Few studies exist that assess the independent risks of subfertility's association with PTB and LBW.[23]

In addition to medical treatments, couples that are experiencing unwanted childlessness might use nonmedical or behavioral interventions. Some of these interventions have data supporting their effectiveness, while others need more research.[24-31] Data exist to support the use of fertility-focused intercourse to increase per-cycle pregnancy rates in couples without evidence of infertility.[32,33] Fertility-focused intercourse approaches include tracking basal body temperatures (BBT), using luteinizing hormone (LH) test kits, monitoring cervical mucus (CM), and counting cycle days using a simple calendar method to predict fertile days. Other nonmedical interventions include losing or gaining weight to achieve a "normal" or healthy body mass index (BMI) and to improve overall health and reproductive capacity.[34] Although different from weight management interventions, another behavioral change that is sometimes reported is the use of fertility diets. Fertility diets typically recommend changing micronutrient profiles to enhance fertility.[35] Couples having difficulty conceiving may turn to complementary

and alternative medicines (CAM). Although there are many CAM approaches that have been explored, some of the more commonly reported fertility-related interventions include the use of vitamins, herbs, and/or acupuncture.[36,37]

1.3 Development of the Fertility Experiences Study

Most of the data available for reproductive outcomes of fertility treatments are biased. Data that are collected from patients enrolled from specialty fertility clinics are likely not representative of all women and couples seeking to become pregnant, selection bias, because many couples seek treatment from other types of providers.[4,38,39] Similarly, many studies focus on outcomes for treatment with assisted reproductive technologies (ART), which complete early stages of human reproduction in vitro, but fewer studies address outcomes for non-ART fertility treatments, and fewer still for spontaneous conceptions among subfertile couples, information bias.[40] Inferences about effects associated with specific treatments require appropriate comparisons to other subfertile couples receiving other treatments, or no treatment.[38,41,42]

To address these gaps, we conducted an observational, retrospective cohort study with parallel clinic-based and population-based cohorts of women residing in the state of Utah, who had a history of primary infertility (i.e., trying to conceive for at least one year, with no prior pregnancies) as of an index date between 2004 and 2008. The clinic-based cohort was recruited from the two major specialty fertility clinics in Utah during the time of the study, while the population-based cohort of women was recruited based on sampling from a linked database of state marriage and birth records.

1.3.1 Methods

1.3.1.1 Design and target populations

The Fertility Experiences Study (FES) consists of two retrospective cohorts. For the clinic-based cohort, we sought to enroll women seen for an initial visit for primary subfertility at one of the two participating fertility specialty clinics during specific time frames within 2004-2008: the Utah Center for Reproductive Medicine (UCRM), affiliated with the University of Utah, or the Reproductive Care Center (RCC), a private practice. Both practices are located in the Salt Lake City metropolitan area and serve a referral base that includes the entire state of Utah. For the population-based cohort, we sought women from the entire state of Utah who had also experienced primary subfertility in parallel time frames.

1.3.1.2 Preliminary eligibility

All potential participants had to meet initial eligibility criteria prior to recruitment, as shown in Table 1.1. At the UCRM, 2 index years were chosen: 2004 and 2008. For RCC, the range of 2000-2009, inclusive, was chosen. Clinic records were used to determine preliminary eligibility for these women. We attempted to contact all women meeting preliminary eligibility criteria for the UCRM 2004 clinic sample and the RCC sample. We attempted to contact a random sample of women from the UCRM 2008 cohort.

For the population cohort, preliminary eligibility was determined from records within the Utah Population Database (UPDB); marriage and divorce records were linked to birth certificates and fetal death certificates, with contact information coming from

various public records linked by the UPDB, including drivers' license renewals. Preliminary criteria were designed to identify married women who remained in partnership, continued as Utah residents, and had no identified birth or fetal death within 2-5 years of the marriage date. The population cohort had two period subcohorts: one with an index date of December 31, 2004, and the other with an index date of December 31, 2008. Within each of these subcohorts, UPDB generated a random sample of women meeting preliminary eligibility criteria, to be contacted by the independent designated intermediary agency for recruiting participants from the UPDB, called the Resource for Genetic and Epidemiologic research.

1.3.1.3 Recruitment and screening

All potential participants were sent a letter by mail, explaining the study and inviting them to respond regarding their interest in the study. Potential participants in the clinic cohort received a letter from their clinic, signed by the director of the clinic and the principal investigator for the study (JBS). This letter invited them to respond to study personnel by phone or email or go directly to a web-based response page. Response options included immediately completing the screening questionnaire (for phone or email), requesting further information, or requesting not to be contacted further about the study. Study staff tracked bad mailing addresses and attempted to make follow up telephone calls for women from UCRM. Due to clinic staffing limitations no address tracking or telephone calls were made for women from RCC.

Potential participants in the population cohort received a mailed letter from RGE explaining the study and inviting them to respond regarding their interest in the study.

They were invited to respond to RGE by mail, telephone, or online web form. Response options included requesting their contact information to be given to study personnel, or requesting not to be contacted further about the study. For women interested in participating, their contact information was given to study staff, who subsequently invited them to be screened for final eligibility. RGE staff also tracked bad mailing addresses and attempted to contact by telephone those women who did not respond to the initial letter from RGE.

1.3.1.4 Final eligibility, enrollment, and consent

All potential participants completed the screening questionnaire by telephone or a web form, using Opinio software. The screening questionnaire took less than 5 minutes to complete. Final eligibility criteria were the same for both the clinic and population cohorts and are shown in Table 1.2. These criteria were designed to identify women with primary subfertility at their index date for the study, who had at least 3 consecutive years of residence in Utah after the index date.

Women who met final eligibility criteria were immediately invited to participate in the study. Enrollment in the study consisted of completing the initial portion of the study questionnaire, described further below. In the first screens of the online questionnaire, the study procedures were explained, and women were informed that completing the questionnaire constituted their informed consent. The study was reviewed and approved by the University of Utah Institutional Review Board for research involving human subjects.

1.3.1.5 Duplicate participants between cohorts

Duplicates participants between cohorts (including the two clinical subcohorts) were possible. During screening some respondents notified us that they had previously participated in the study; in these cases, we retained their first response only. After responses from all cohorts were received, we identified remaining duplicate responses by name, birthdate, or email address. In this way, we identified five additional duplicates: three that had responded to both the population invitation and the UCRM invitation and two that had responded to both the population invitation and the RCC invitation. For these five women, we utilized the data from the responses given to the clinic invitation. Although some women had received care at both UCRM and RCC, they responded to only one clinic invitation: we identified no duplicates between the clinic cohorts using name, birthdate, or email address.

1.3.1.6 Design of the questionnaire

We initially conducted a literature review to identify questionnaires that possibly included domains of interest for our research (Table 1.3). [43-53] We also contacted authors to obtain copies of their instruments, where possible. We used items verbatim from some questionnaires.[44,45] Based on this review and consultation with experts in the field, we constructed a questionnaire with the domains of interest for our research, called here the Fertility Experiences Questionnaire (FEQ).

1.3.1.7 Pilot testing

We pilot tested the FEQ in four sequential phases by self-administration (written), by face-to-face interview, by telephone interview, and by mixed-mode of administration (written, followed by interview). Revisions of wording of some items and responses were undertaken, informed by each phase. A total of 17 current patients of UCRM were included in the pilot testing. Based on the pilot work, we found that mixed-mode administration was most efficient to yield complete and internally consistent information on attempts to conceive (as described further below). We also found that we had more complete and internally consistent information regarding pregnancy outcomes, fertility treatments, and self-help measures when these were likewise assessed first in writing, with a follow-up telephone interview.

1.3.1.8 Data Collection

Participation in this study consisted of completing a mixed-mode, two-part questionnaire, the Fertility Experiences Questionnaire (FEQ). The first phase of the FEQ was administered via the internet, using Opinio software, taking 25-45 minutes to complete. In a few cases, women completed a paper questionnaire and returned it by mail. The second phase was an in-depth phone interview conducted by trained study staff, requiring between 20 and 45 minutes to complete.

In both phases of the FEQ, quantitative and qualitative data were collected, including reproductive history, fertility treatment history, feelings surrounding infertility and treatments, treatment choices, and pregnancy outcomes that directly resulted from each attempt. After study data collection was complete, we mailed a letter to all study

participants informing them that we planned to link their study data to Utah vital records for birth certificates and fetal death certificates. Only seven individuals opted out of the linkage section of the study. The UPDB linked enrolled participants to vital records and data from the Utah Birth Defects Network. Women who completed both the online and telephone portions of the FES were sent a $10 gift card for a local grocery store, with a handwritten thank you note from the study staff.

1.4 Validation of FES Questionnaires

Our goal, with the creation of the FEQ, was to generate an instrument that can be used retrospectively to ascertain fertility treatments chosen by women, reasons for choosing or declining different treatments, factors that may have influenced choices of treatments, timing of treatments, and a detailed history of attempts to conceive (by which we mean time at risk of pregnancy, as defined further below). We conducted a validation comparing components of the questionnaire with data from medical records in a clinical sample.

1.4.1 Attempts to conceive or time at risk of pregnancy

The "pregnancies and attempts to conceive" component of the FEQ captures information about all time in a woman's life when she was at risk of pregnancy, whether or not she was "trying" to conceive, and whether or not the "attempt" ended in pregnancy. Each time period at risk of pregnancy is called an "attempt" to conceive in the FEQ. The written questionnaire contains a definition as well as an illustrative example for "attempts to conceive" to enhance respondents' understanding of the concept

of "attempts to conceive." Several initial questions are asked in the written questionnaire, with a follow-up telephone interview for further verification and clarification. The goal is to capture as accurately as possible the time a woman was actually at risk of pregnancy. Unlike other time to pregnancy (TTP) questions that ask a woman to report a general number of months it took to become pregnant, the "attempts to conceive" section specifically excludes time that a woman was not at risk for pregnancy (for example, due to spousal separation, or desire not to have a baby in a certain month), even though she may have intended to achieve a pregnancy.[54] It also explicitly includes time that a woman was at risk of pregnancy without intending pregnancy.[55] This issue is explored in detail in Aim 1 of this dissertation.

1.4.2 Validation Methods

This validation includes two groups of women (see Figure 1.1). The original group was selected via random sample of women over the age of 18 who had an initial consultation for subfertility generally, or in vitro fertilization (IVF) specifically at the UCRM in the year 2004. Women who completed the online questionnaire were contacted by telephone for the follow-up interview at a time of their convenience to conduct the telephone component of the FEQ. The follow up interview typically occurred within 2 weeks of completion of the written survey. Medical records were then obtained from the UCRM for independent chart review to extract key variables for comparison. Records from any other clinics that patients may have visited in addition to UCRM were not available to us for analysis. For the validation, we chose the following variables to compare between the medical chart review and the FEQ: use of oral ovulation enhancing

drugs, use of injectable ovulation drugs, use of IUI, use of IVF, time at risk of pregnancy, time to conception, pregnancy, and live birth. These represent the outcomes of greatest interest for this questionnaire.

We performed correlation analyses to determine the degree of agreement between the specified elements in the FEQ and the patients' medical records. For categorical variables (history of different types of treatment and pregnancy history), we calculated sensitivity and specificity, and used the kappa statistic to rate interobserver agreement. [56]

1.4.3 Treatment history

The agreement between the FEQ and the medical record for different treatments is shown in Table 1.4. Compared to the medical record, the sensitivity of the FEQ was uniformly higher than specificity. The agreement was good for IUI and ART (kappa 0.64, 95% CI 0.46-0.83; and 0.74, 95% CI 0.57-0.90, respectively), but lower for use of oral ovulation drugs and injectable ovulation drugs (0.41, 95% CI 0.21-0.61 and 0.21,95% CI 0.0-0.51, respectively).

1.4.4 Pregnancy history

The kappa for the agreement for pregnancy history during the time the woman was a patient at the clinic was 0.65. There was perfect concordance for 50 (79.4%) participants with respect to the number of pregnancies reported in the interview with the number of pregnancies reported in the medical record. Nine women (14.3%) reported more pregnancies in the interview than were reported in the medical record, while one (1.6%) reported one fewer pregnancy in the interview than was reported in the medical

record. The kappa for the agreement between live births a woman had during the time she was a patient at UCRM and what she reported was 0.55. Forty-three (68.3%) showed perfect concordance, while 12 (19%) reported more live births in the interview than in the medical record and one (1.6%) women reported one fewer live birth in the interview than in the medical record.

1.4.4 Time at risk of pregnancy and to time to conception

About half of the medical records did not contain sufficiently detailed information on time attempting to conceive at the first visit. We were able to compare and calculate time at risk of pregnancy for 35 women and time to conception for 29 of those women. The mean and median time at risk for pregnancy, as reported in the interviews was 42.1 months and 40 months, respectively; in the medical record it was 36.4 and 30, respectively, with a Pearson's correlation coefficient of 0.42 (95% CI 0.10-0.66) (Table 1.5). For time to conception, the Pearson's correlation coefficient was 0.77 (95% CI 0.55-0.88.

In this validation study, we found that women's responses to the FEQ were reasonably comparable to medical records for total time at risk of pregnancy, time to conception, pregnancy, live birth, and the use of IVF and artificial insemination. However, there was poor correlation between the FEQ and medical records for the use of oral or injectable ovulation drugs. Uniformly, sensitivity was higher than specificity, meaning that women reported many treatments or events that were not found in the medical record. This may mean that some women may have obtained treatments from physicians outside of the UCRM at the same time that they were also being seen at

UCRM, that women did not recall the timing correctly for treatments that were used before or after their time at UCRM, that women misunderstood what was meant by the questions (despite the fact that examples were given), or it may mean that the use of some treatments was not completely recorded in the medical record. Underreporting in the medical record of treatments actually given at the UCRM is possible for drugs, but we believe it is much less likely for procedures such as artificial insemination or IVF.

Although there was substantial agreement in regards to pregnancies a woman achieved while as a patient in the clinic, nine (14%) of the women interviewed reported having more pregnancies at the time they were patients at UCRM than those recorded in their medical record. This is consistent with the fact that after receiving fertility treatment at the UCRM, some women go to their own OB/GYNs, family physicians, or midwives to confirm a pregnancy and receive prenatal care (since prenatal care is not provided at the UCRM). Unless there is some subsequent contact between the women and the UCRM, these pregnancies do not end up in the UCRM records. During this time period, there was routine follow-up from UCRM to women or couples undergoing IVF, but not necessarily for women undergoing other types of fertility treatment. Probably for the same reasons, many women who had live births reported more live births in their interviews than what was found in their medical record at the UCRM. Additional validation studies that allow linkage to medical records of *all* providers seen, or perhaps complete visit and pharmacy billing records, are needed to corroborate our hypothesis that women reported additional fertility treatment and care for pregnancy outside of the single specialty clinic studied.

In the development and pilot testing of the FEQ, we found that a combination of

written or online questions, followed by a clarifying telephone interview seemed to assure adequate understanding of the concept of "attempt to conceive." While this makes the mixed-mode FEQ more resource-intensive to administer than an online-only (or written-only) questionnaire, we expect it may be worthwhile to collect this detailed information on time at risk of pregnancy. While TTP assessed retrospectively may be subject to recall bias, others have shown that the reliability of TTP recall is enhanced when women are queried in-person or via telephone or e-mail.[54,57,58] We believe this supports the value of the two-stage approach to assessing TTP we have employed in the FEQ.

We believe that the FEQ captures a more accurate and complete time at risk of pregnancy (called "attempts to conceive" in the FEQ) than the single measure of time "trying to conceive" reported in the woman's medical record, as evidenced by the 35 (52%) women in our sample that reported multiple attempts in the time leading up to the first clinic visit (for which the clinic visit identified only one "time trying" to conceive).

1.5 Description of Population and Clinic Cohorts

A total of 26,007 letters were sent, 15,400 for population recruitment and 10,677 for clinic recruitment. There was no response to 22,758 (87%) of the letters and only 153 (<1%) refused participation without screening. A total of 3,166 (12%) replied as interested in learning more about the study. Nearly all (96%) interested women were contacted for screening. Only 36% were eligible for participation based on living in Utah during the index period, not having any prior pregnancies, and trying to conceive for at least 12 months without conception. Of the 1105 eligible women, 87% (960) enrolled and

completed the online portion of the study. Table 1.6 describes the characteristics of all of the enrolled women by recruitment cohort. Although 903 women began the phone portion of the interview, only 837 completed all of the necessary parts. Figures 1.2 and 1.3 show the recruitment flow for each of the recruitment cohorts.

1.5.1 Description of Population Cohort

A total of 501 women from the population recruitment cohort enrolled in FES. The majority of women were between the ages of 18 and 30 at their index date with only 6% over the age of 30 and no one over the age of 35. Most women (95%) identified as white, non-Hispanic and either had some college or had graduated from college. The average longest attempt duration was 3.3 years (SD 2.8; median 3 years; range < 1 year-16 years). Over half 53.5% had had a live birth by the time we interviewed them for the study. Using mutually exclusive categories to group women by their most invasive treatment: close to a third (31.3%) had never received any type of fertility treatment, 5% reported trying alternative treatments, 29% had used fertility drugs, 20% had used artificial insemination, and 14% had used IVF.

1.5.2 Description of Clinic Cohort

A total of 459 women from the clinic recruitment cohort enrolled in FES. Women recruited from the clinic were older on average than those from the population ($p < 0.001$). Most women (93%) identified as white, non-Hispanic and either had some college or had graduated from college. The average longest attempt duration was 4.2 years (SD 3.4; median 3 years; range < 1 year-18 years). Over half 58% had had a live

birth by the time we interviewed them for the study, and women from the clinic cohort reported close to double the number of multiple births (14.4% compared to 6.6% from population; $p < 0.001$). Using mutually exclusive categories to group women by their most invasive treatment: Only 6.5% had never received any type of fertility treatment and 1.7% reported trying alternative treatments, 15.9% had used fertility drugs, 29% had used artificial insemination, and 47.3% had used IVF.

1.6 Overall Motivation and Summary of Chapters

The data from the Fertility Experiences Study provide in-depth detail on reproductive histories of a cohort of subfertile women. The novel recruitment approach fills a gap in current approaches to fertility research that involves women who may not have been seen in fertility clinics. The rich data allow for robust exploration into how women report their time at risk for pregnancy, nonmedical and medical treatments used during their reproductive history, and associations between fertility treatment and preterm births compared to subfertile women conceiving spontaneously.

The duration of time attempting pregnancy, or time at risk of pregnancy (TARP), is central to the definition of infertility, but they can be defined and assessed in different ways. Aim 1 examines how women with a history of primary infertility recall their attempt duration or TARP, when asked with different questions. Misestimation of attempt duration could have important clinical implications. Understanding how women report TARP has the potential to improve the quality of data collected about pregnancy attempt durations in future research studies and to ensure appropriate management in clinical settings.[59] Appropriate management could help avoid use of treatment with more

invasive, high-cost medical therapies such as IUI or IVF before such treatment is clinically warranted.[6,60] Clinicians and researchers should recognize the limits of single question when assessing how long a couple has been having regular unprotected intercourse. Detailed attempt histories can capture a more detailed assessment of time at risk of pregnancy.

Aim 2 describes use of behavioral, nonmedical, and medical interventions reported by women who experienced primary infertility. Women were asked about the use of interventions used to enhance fertility, either on their own or by recommendation of a doctor. Women were asked about the use of interventions used to enhance fertility, either on their own or by recommendation of a doctor. Interventions included fertility-focused intercourse (by basal body temperature, cervical fluid, urine LH, and/or counting days); behavioral changes (weight loss, adherence to fertility diets); complementary and alternative medicine (CAM: vitamins, herbs, and/or acupuncture); and medical treatments (ovulation stimulation drugs (OS), IUI, and/or IVF with or without intracytoplasmic sperm injections (ICSI)). We also assessed male partner treatments in a subgroup of participants. This mix of medical and nonmedical interventions while trying to conceive has not been described previously. This is also one of the first studies to assess nonmedical interventions engaged in by the male partner of the subfertile couple.

Aim 3 examines the effect of fertility treatment OS alone, IUI usually with OS, and IVF on PTB, compared to no treatment in subfertile women. While some providers advocate that IVF should become a primary management strategy for couples without specific indications because of its high probability of success per cycle success, there are substantial concerns about expanding use of IVF, including high cost and impact on

neonatal outcomes.[15,16] Epidemiologic studies have demonstrated higher incidence of PTB, LBW, and birth defects among children conceived through IVF, when compared to children conceived naturally, even when the analyses are limited to singleton pregnancies.[21,23,61] Additional questions remain as to whether these adverse outcomes are related to the treatments or to the underlying causes or severity of the subfertility.[21,22] Few studies exist that assess the independent risks of subfertility.[23] Aim 3 provides insight into the relationship between fertility treatments (OS, IUI, and IVF) and preterm birth among women with primary subfertility compared to subfertile women who conceived without fertility treatment. We used data from parallel clinic and population-based cohorts and examined the contribution of pregnancy attempt duration and fertility-related diagnoses, as well as the role of multiple gestations.

The final chapter will summarize key findings from the three aims, discuss practice implications, and outline recommendations for future research directions.

Table 1.1 Preliminary eligibility criteria

Clinic Cohort
New patient for infertility at UCRM in 2004 or 2008; or RCC between 2000-2009
Patient has a male partner
Age 20-34 at first visit (UCRM only)
No known pregnancies prior to first appointment at clinic (UCRM only)
Population Cohort (*consists of two period subcohorts (a) and (b)****)***
Married between (a) January 1, 2000, and December 31, 2002, or (b) between January 1, 2004 and December 31, 2006
Age 18-30 at date of marriage
Married 2-5 years to same person as of (a) December 31, 2004, or (b) December 31, 2008
Husband living as of (a) December 31, 2004, or (b) December 31, 2008
No Utah live births or fetal deaths as of (a) December 31, 2004, or (b) December 31, 2008
Current Utah address within the past 5 years

Table 1.2 Final eligibility criteria for both the clinic cohort and the population cohort

Age 20-35 at index date Clinic cohort: date of first clinic visit Population cohort: (a) December 31, 2004, or (b) December 31, 2008
No pregnancies prior to index date
At least one year of trying to get pregnant with male partner at index date
Residence in Utah during entire three years following index date

Table 1.3. Domains and components in the Fertility Experiences Questionnaire

Domains	Written component (paper or online)	Phone interview component
General health	X	
Menstrual history	X	
Sexual history	X	
Pregnancies and attempts to conceive	Definitions and list of attempts	Verification and detailed questions about attempts
Pregnancy outcomes	Dates and types of outcomes	Verification and details
Fertility-related medical evaluations	X	
Fertility-related diagnoses	X	
Fertility-related surgeries	X	
Fertility treatments used, and reasons for choosing or declining treatments	X	Details about treatments received, and linking timing to attempts to conceive
Self-help measures for trying to conceive (fertility awareness, diet, etc.)		Ascertained and linked to attempts to conceive
Experience of fertility treatment	X	
Stress and social situation	X	
Adoption experiences	X	
Demographic information	X	
Friends and family with infertility	X	
Wantedness of pregnancies prior to conception		X
Hypothetical interest in participating in studies of fertility treatment		X

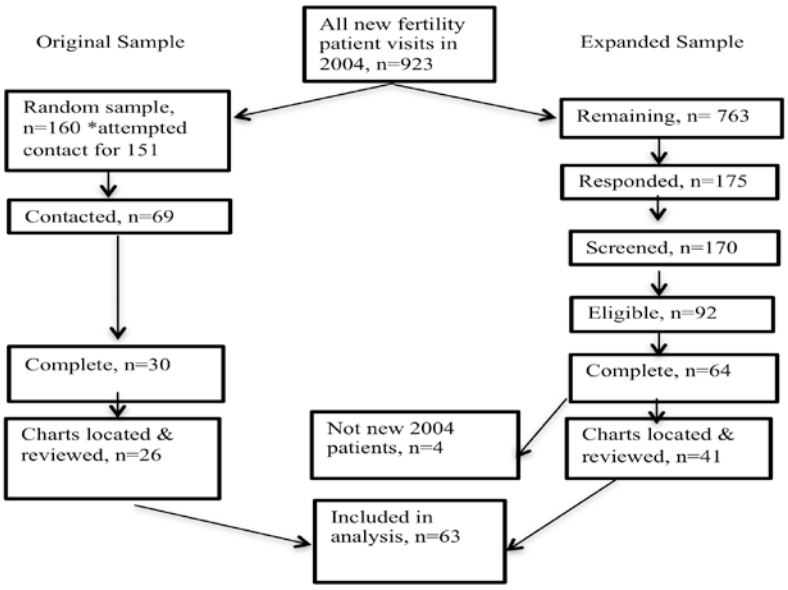

Figure 1.1 Validation study flowchart

Table 1.4 Agreement between medical record review and FEQ interview for fertility treatments, and sensitivity and specificity of the FEQ interview, considering the medical record as the gold standard

Ovulation drugs, oral				**Kappa [95% CI]**	**Sensitivity[95% CI]**	**Specificity [95% CI]**
		Interview				
		Yes	**No**	0.41 [0.23-0.93]	91% [80-100]	55% [39-71]
Medical Record	**Yes**	21	2			
	No	17	21			
Ovulation drugs, injectable						
		Interview				
		Yes	**No**	0.26 [0.03-0.51]	70% [54-85]	57% [39-75]
Medical Record	**Yes**	23	10			
	No	12	16			
Intrauterine insemination						
		Interview				
		Yes	**No**	0.64 [0.46-0.83]	93% [83-100]	69% [59-88]
Medical Record	**Yes**	25	2			
	No	9	25			
In Vitro Fertilization						
		Interview				
		Yes	**No**	0.74 [0.57-0.90]	96% [88-100]	82% [69-94]
Medical Record	**Yes**	23	1			
	No	7	30			
Pregnancy						
		Interview				
		Yes	**No**	0.65 [0.47-0.84]	97% [91-100]	67% [49-84]
Medical Record	**Yes**	32	1			
	No	9	18			
Live Birth						
		Interview				
		Yes	**No**	0.55 [0.36-0.75]	96% [87-100]	64% [47-80]
Medical Record	**Yes**	22	1			
	No	12	21			

*Some items were missing in the medical record for some patients, so actual number for each item is less than 63.

Table 1.5 Correlation between medical record review and interview for duration of time at risk of pregnancy and time to conception

	Source	Mean Months (SD)	Median Months	Range, Months	Correlation [95% CI]
Time at risk of pregnancy, n=35	Interview	42.1 (22.5)	40	7-117	0.42 [0.10-0.66]
	Medical record	36.4 (21.7)	30	5-96	
Time to conception, n=29	Interview	40.5 (20.8)	38	14-117	0.77 [0.55-0.88]
	Medical record	36.4 (22.3)	29	5-96	

Table 1.6 Characteristics of enrolled women (N = 960)

	Clinic		Population		Total		p-value
	N	%	N	%	N	%	
Age At Index Date							0.000
18-<25	206	56.9%	317	73.2%	523	65.8%	
25-<30	110	30.4%	107	24.7%	217	27.3%	
30+	46	12.7%	9	2.1%	55	6.9%	
Annual Income							0.000
Less than $50,000	112	25.6%	180	37.3%	292	31.7%	
$50,000-$99,999	247	56.4%	259	53.7%	506	55.0%	
Over $100,000	79	18.0%	43	8.9%	122	13.3%	
Education Level							0.298
Less than college graduation	163	35.7%	195	38.9%	358	37.4%	
College graduation or more	294	64.3%	306	61.1%	600	62.6%	
Race/Ethnicity							0.200
White	425	92.6%	474	94.6%	899	93.7%	
Hispanic, Other Non-White	34	7.4%	27	5.4%	61	6.4%	
Religious Affiliation							0.081
Latter-day Saint	121	26.4%	108	21.6%	229	23.9%	
Non-LDS	338	73.6%	393	78.4%	731	76.2%	
Maximum Insurance							0.000
None or unsure	32	7.4%	59	13.6%	91	10.5%	
Diagnostic and/or Treatment	100	23.1%	172	39.6%	272	31.4%	
Not Asked	301	69.5%	203	46.8%	504	58.1%	
BMI Category							0.276
Underweight/Normal	220	52.3%	223	48.6%	443	50.3%	
Overweight/Obese	201	47.7%	236	51.4%	437	49.7%	
Ever Pregnant							0.034
No	117	44.0%	149	32.8%	266	29.6%	
Yes	328	51.7%	306	67.3%	634	70.4%	
Ever Live Birth							0.019
No	156	35.1%	193	42.7%	349	38.9%	
Yes	289	64.9%	259	57.3%	548	61.1%	
Highest Treatment (Screen)							0.000
None	43	9.4%	207	41.3%	250	26.0%	
Ovulation Drugs	63	13.7%	128	25.6%	191	19.9%	
IUI	142	30.9%	97	19.4%	239	24.9%	
IVF	211	46.0%	69	13.8%	280	29.2%	
Longest duration (screen)							0.068
12mo-<24months	55	31.3%	84	16.8%	139	14.5%	
24mo-<48months	155	33.8%	154	30.7%	309	32.2%	
48mo-<60months	50	10.9%	65	13.0%	115	12.0%	
More than 60 months	195	42.5%	185	36.9%	380	39.6%	
Total	459	47.8%	501	52.2%	**960**	**100.0%**	

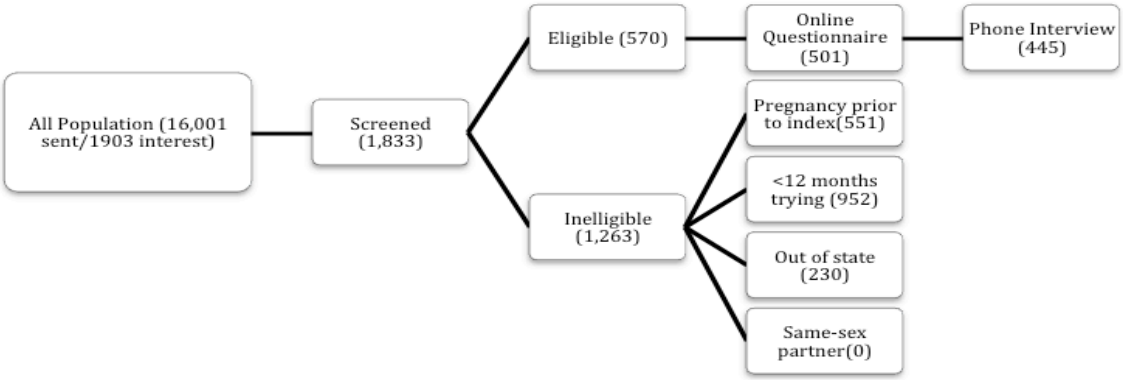

Figure 1.2 Recruitment flowchart for population cohort

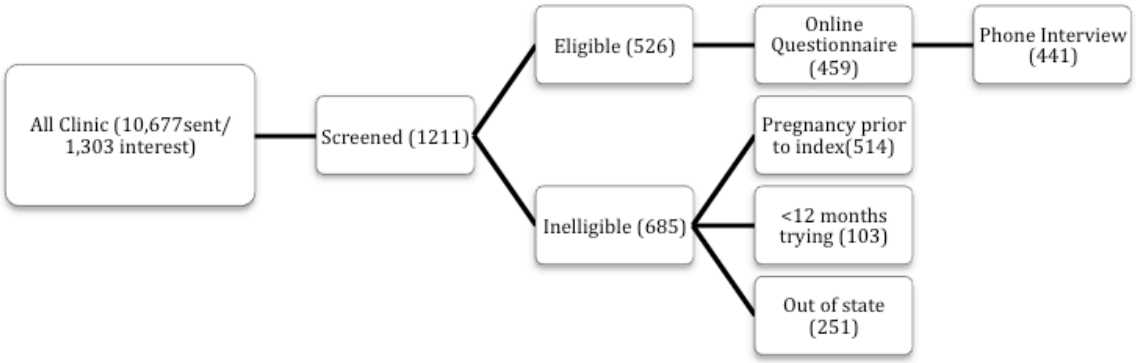

Figure 1.3 Recruitment flowchart for clinic cohort

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CHAPTER 2

A COMPARISON OF THREE APPROACHES TO COLLECTING DATA ON PREGNANCY ATTEMPT DURATION AMONG WOMEN WITH A HISTORY OF PRIMARY SUBFERTILITY

2.1 Abstract

The duration of time attempting pregnancy, or time at risk of pregnancy (TARP), are central to the definition of infertility (or subfertility), but they can be defined and assessed in different ways. The aim of this study is to examine how women with a history of primary subfertility recall their attempt duration or TARP when asked with different questions.

The Fertility Experiences Study (FES) is a retrospective cohort study of women with primary subfertility conducted at the University of Utah between April 2010 and September 2012. Questions about pregnancy attempt duration were repeated over the course of the FES at different times using three different approaches: a single question, a series of specific questions about dates (date approach), and a question about dates of "actively trying."

We found significant discrepancies in reported attempt duration between the three approaches. Only a third (34%) of women accurately reported their longest attempt

duration based on a single question, as compared to information obtained using the date-based approach (+/- 3 months), while 37% of women overestimated and 29% of women underestimated their TARP with the single question. However, for a 24-month threshold, the single question was over 90% correct compared to the date-based approach. Asking about the date of actively trying resulted in shorter attempt durations.

Clinicians and researchers should recognize the limits of single question when assessing how long a couple has been having regular unprotected intercourse. Detailed attempt histories can capture a more nuanced assessment of time at risk of pregnancy.

2.2 Introduction

One in seven couples will experience difficulty conceiving at some point in their reproductive lives.[1, 2] The International Committee for Monitoring Assisted Reproductive Technology (ICMART) define infertility as a disease of the reproductive system resulting in the failure to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse.[3] This definition of infertility—as failure to achieve pregnancy after 12 months with unprotected intercourse has been widely used in both research and clinical settings. Although the term infertility is frequently used to describe the clinical condition, the use of the term subfertility may be more accurate in expressing the spectrum of fertility that many couples experience. Subfertility will be used for the purposes of this manuscript.

Pregnancy "attempt duration" is an important concept as it is central to how subfertility is defined and diagnosed. Extended attempt duration it also an independent predictor of more severe subfertility and of adverse pregnancy outcomes.[4] When

examining fecundity (defined as the biologic capacity to reproduce) it is important to consider that many couples will successfully conceive without medical treatment even after meeting the criterion for clinical subfertility. Among couples with unexplained subfertility, an estimated 43-60% of those who fail to conceive during the first 12 cycles will achieve conception after an additional 12 cycles of trying, depending on age.[5] Therefore, the World Health Organization (WHO) has recommended using a definition of subfertility of 24 months of unprotected intercourse to reduce the number of individuals who are "falsely" diagnosed with fertility problems.[6] Beyond the 24 months there is still a small potential for spontaneous conception without medical assistance.[3, 7] However, couples who do not conceive after 48 months of properly timed intercourse have more severe subfertility, and the likelihood of spontaneous conception without treatment drops to only 5%.[7]

Given that attempt duration is a central component of subfertility diagnosis, differences in how researchers and clinicians collect data on biological "time at risk for pregnancy" (TARP), intentional pregnancy attempt duration, or behavioral time "actively" trying to conceive can influence key findings in the field and how clinical management proceeds. Additionally, all of the measures of pregnancy attempt duration are patient-reported and therefore subject to typical biases including recall error, social desirability, and accuracy. Methods should be addressed to reduce these biases. There has been movement among the scientific community to increase the monitoring of fertility using more direct and consistent measures of biological TARP rather than measures of "trying to conceive" which implies intention.[8-10]

Understanding how women report TARP has the potential to improve the quality

of data collected about pregnancy attempt durations in future research studies and to ensure appropriate management in clinical settings.[11] Appropriate management could help avoid use of treatment with more invasive, high-cost medical therapies such as intrauterine inseminations (IUI) or in vitro fertilization (IVF) before such treatment is clinically warranted.[12, 13] Additionally, identifying characteristics of women who substantially misestimate (either over- or underestimate) TARP may provide insight on the reliability of single question approaches frequently used in clinical practice and the potential for bias caused by differential misclassification of the severity of subfertility for women reporting fertility histories.

The aim of this study is to compare longest pregnancy attempt recall based on three different questioning approaches among women with a history of subfertility. The first approach uses a standard single question (single question approach); the second approach is a series of questions assessing discrete pregnancy attempts using specific dates for start and stop time at risk (date approach), and the third approach asks the woman for a date when she began "actively" trying to become pregnant (active date approach). In this study, the date (second) approach is used as the "gold standard" for TARP and used to compare to the other approaches. We hypothesize that women frequently misestimate TARP when using a single question approach, as compared to the approach based on dates.

2.3 Methods

The Fertility Experiences Study (FES) is a retrospective cohort study conducted at the University of Utah between April 2010 and September 2012. The FES cohort was

developed with the intention of identifying women with primary subfertility who may or may not have received clinical diagnosis or medical treatment. Women were recruited from fertility clinics as well as from the general population. The clinic-based cohort was recruited from two specialty fertility clinics in Utah. For clinic recruitment, invitations were mailed to all women who had initial clinic visits during the index years of 2004 and 2008. The population-based cohort was identified using a unique research resource called the Utah Population Database (UPDB). The UPDB is a database that links vital records and medical records and provides access to present and historical information on over 7 million individuals. Using the UPDB, we were able to sample state marriage records without linked birth certificates or fetal death records within two years of their marriage. Recruitment of the population-based group was facilitated by the Resource for Genetic and Epidemiologic Research (RGE) to maintain the privacy of individuals and confidentiality of data belonging to women who were not interested in enrolling. RGE mailed letters and followed up with telephone calls to inform potential participants about the study. Interested individuals from both the population and clinic recruitment were screened for eligibility. The parallel clinic-based and population-based cohorts consist of women residing in Utah with a history of primary subfertility (i.e., trying to conceive for at least 1 year, with no prior pregnancies) as of a specified index date between 2004 and 2008. Women from both cohorts were screened for eligibility. Women determined to be eligible were then invited to complete a self-administered online questionnaire (or paper, if requested). Upon completion of the self-administered questionnaire, trained study staff conducted an in-depth phone interview. Upon completion of the study participants received a $10 gift card. A multidisciplinary team of clinicians and researchers developed

both the self-administered questionnaire and the phone interview tool. The questionnaire was validated using a sample of clinic-recruited women prior to initiating the study. Questionnaire data on pregnancy attempt duration, medical treatment, attempt outcomes, and pregnancy outcomes were compared with medical records from one of the specialty clinics the Utah Center for Reproductive Medicine (UCRM). Compared to the medical record, the Fertility Experiences Questionnaire (FEQ) was over 90% sensitive for all elements, except injectable ovulation drugs (70% sensitivity). The FEQ accurately captured many elements of fertility treatment history at 5-6 years after the first visit to a specialty clinic. The University of Utah Institutional Review Board approved this study.

The three different approaches to assessing pregnancy attempt duration were based on different questions asked at different times during the study. The first approach, used during the participant screening process, was designed to identify women who may have experienced primary subfertility with a single question. This "*single question approach"* question was worded "What was the longest period of time where you were not doing anything to prevent pregnancy but did not get pregnant?" The second approach, "*the date approach,"* asked about specific dates when participants were at risk for pregnancy, defined as time intervals when they were having sexual intercourse with a man without using any method to prevent pregnancy. The date approach was designed to identify more precise time periods when a woman was biologically *at risk* for pregnancy and to exclude periods when she was using birth control or was not heterosexually active for any reason. Pregnancy attempts started when the woman started becoming heterosexually active without birth control, or simply stopped using birth control. Pregnancy attempts could end in pregnancy, use of birth control, separation or divorce

from partner, or abstinence from intercourse for any other reasons. These questions were asked in the online survey and then repeated and verified during the telephone interview. A third approach, "*the active date approach,"* was asked during the telephone interview to specify when couples were actively trying to conceive. This approach asked women "Was there a point during this attempt when you 'actively' started trying to get pregnant? What date did you actively start trying to get pregnant?" The active attempt duration used the same end date as described in the second approach. For the purpose of this analysis, each discrete attempt was assessed to determine longest discrete pregnancy attempt durations. Only the longest reported duration was used in the analysis as a comparison to the single item question.

Descriptive analysis was performed to determine characteristics of women who substantially misestimated their longest reported TARP with the use of the single question approach, as compared to a date-based approach (considered the "gold standard" for this analysis). Substantial misestimation was defined as a difference of 3-months or more between the single question and date-based approach. Participant characteristics examined were recruitment pool (population or clinic), months since first pregnancy attempt began, having a pregnancy or live birth during the follow-up period of the study, participant utilization of memory aids (including medical chart, journals, or diaries) during data collection, self-perception of subfertility, and sociodemographic characteristics (age at study index, BMI, income, education, race/ethnicity, and religious affiliation). Pearson's chi-squared tests were used to assess the proportion of women misestimating TARP by different characteristics. A multinomial logistic regression analysis was conducted to calculate unadjusted and adjusted relative-risk ratios (RRR) to

separately estimate the risk of TARP overestimation and TARP underestimation associated with a variety of factors. Potential confounders, including recruitment site, age, BMI, education, and religious affiliation, and months between attempt initiation and date of interview were determined a priori and were adjusted for in all multivariable models to determine adjusted relative-risk ratios (aRRR). We developed three models to assess the relative risk of TARP misestimation: Model 1 included recruitment site, age, BMI, education, and religious affiliation, as well as months between the date of the first attempt initiation (based on the date approach) and interview; Model 2 included all aforementioned variables in addition to pregnancy outcomes; and Model 3 included previous covariates and the most invasive fertility treatment used during all pregnancy attempts. A sensitivity analysis was conducted limiting to longest durations that were reported as first attempts only.

Additional analyses were conducted to examine the variation in TARP reported by the participants in the FES study using all three approaches to assess the single longest attempt duration. A Pearson's correlation is used to examine the relationship between the single question approach, the date approach, and the active date approach. Distributions of the single longest reported attempt durations from each of the three questions approaches were examined with regard to different thresholds for subfertility: subclinical (<12 mo), clinical (≥12 mo), WHO recommendation (≥24 mo), and more severe subfertility (≥ 48 mo). Sensitivity and specificity for the three approaches were used to examine consistent assignment to above subfertility thresholds.

2.4 Results

A total of 960 women enrolled in FES: 501 women were recruited from the population and 459 women were recruited from fertility clinics. Completion rates were good, with 886 (92%) women completed both the online survey and the phone interview. Of women who completed the study, 19 women were dropped from the analysis due to missing attempt data; four of these women had dates that were improperly formatted in the database, and 15 women had missing attempt end dates but had not reported that they were "still trying to conceive." A total of 867 women were retained for data analysis. Figure 2.1 describes the participant flow for the study and analysis.

Women recruited from the fertility clinics were on average 5.4 years older at the index date compared to women recruited though the population ($p < 0.001$). Women in the clinic cohort were also 1.4 years older at the time of their first attempt than women recruited form the population (25.8 ± 4.8 years versus 24.4± 3.1years; $p < 0.001$). In addition, women from the clinic-cohort reported longer attempt durations with both the single approach and the dated approach compared to the population-cohort. Clinic recruited women reported an average of 60.4 months ± 42 months using the single question approach and 58.7 months ± 41 months using the dated approach ($p < 0.001$). Population recruited women reported an average of 50.9 months ± 32 months using the single question approach and 45.2 months ± 32 months using the dated approach ($p < 0.001$). Women recruited from the clinic also had a significantly longer time between the dates that their first attempt started and when the date the interview was conducted in comparison with women recruited from the population (mean 102 months ± 55 months versus 76 months ± 31 months, respectively; p-value < 0.001).

Most women (82%) reported their single longest attempt began when they first initiated regular intercourse without contraception. There was a statistically significant difference in longest TARP reported using the single question approach compared with the date-based approach. The mean longest single attempt duration was on average 4.5 months longer using the single question compared to the date-based approach (56 months ± 38 versus 52 months ± 38; p-value < 0.001). Overall, women from both recruitment pools overestimated their longest TARP using the single question approach. Women recruited from the clinic overestimated by an average of 1.8 months (± 29 months), while population-recruited women overestimated by 5.7 months (± 26 months; p-value = 0.04).

Over half of the women enrolled in the study had at least one pregnancy ending in a live birth, and 13/49 (26.5%) of the women who had a pregnancy without a live birth were still pregnant at the time of the phone interview. Over two thirds of women who did not achieve a pregnancy (292/435) were still attempting pregnancy at the time of the interview, the remaining third had not achieved pregnancy but reported that they were no longer trying to conceive. Women who never achieved a pregnancy had the longest average single attempt of 71 months ± 42 months, followed by those having pregnancy without a live birth (including women who were pregnant during the interview) 45 months ± 29 months using the date approach. Women who had a pregnancy that resulted in a live birth had the shortest average longest pregnancy attempt duration (40 months ± 29 months) using the date approach.

Table 2.1 displays the proportion of women who accurately reported their TARP on the single question and those who either over or underestimated their TARP by more than 3 months (using the date-based questions as a gold standard) for different

characteristics of the women. Many women in the study (37%) overestimated their longest TARP with the single item approach, about a third (34%) estimated their longest attempt duration accurately using the single question (within 3 months of the date approach), and 29% underestimated their longest attempt duration with the single question. Unadjusted relative risk ratios for associations between misestimating TARP by more than 3 months are reported in Table 2.2. Women who accurately reported their longest TARP and those who misestimated longest TARP differed by recruitment site, age at index, BMI, education level, religious affiliation, attempt outcomes, length of time between start of first attempt and time of interview, and most invasive fertility treatment ever used.

In the adjusted analysis, the expected risk of under- and overestimating longest TARP was increased for each year older women were at the time of their first attempt (RR 1.88 [95% CI 1.27-2.79] and RR 1.04 [95% CI 1.00-2.04], respectively). Women who were overweight or obese were also at an increased risk of overreport TARP than for women who were either normal weight/underweight (RR 1.44 [95% CI 1.01-2.05]). Women who completed college had a lower risk of overestimation, RR 0.64 [95% CI 0.43-0.93], or underestimation, RR 0.57 [95% CI 0.37-0.87], than women with lower educational levels. Women who had longer intervals between the start of their first attempt and were at an increased risk of overestimating their longest attempts for each additional year between their first attempt and the interview, aRRR 1.01 [95% CI 1.00-1.02]. Women who had IVF were also at an increased risk of overestimating their attempt duration compared to women who had any other treatment or no treatment at all aRRR 1.62 [95% CI 1.08-2.44] (Table 2.3).

The Pearson's correlation between TARP reported by the single question approach versus the date approach was 0.73. Using the single question approach and a time trying criterion of 24-months (based on the WHO recommendations) as a cutoff for a diagnosis of subfertility, the sensitivity of the single question approach was 97.5% and the specificity was 56.8%, resulting in 88% being correctly classified as infertile. When using a 48-month cutoff, the single item approach had a 90.4% sensitivity and a 76.7% specific, resulting in 82% being correctly identified as severely infertile. We could not assess for the 12-month cutoff because women with less than 12 months on the single question approach (on the screening questionnaire) were excluded from the study.

The distribution of attempt duration by each method of questioning, divided into four categories, is seen in Figure 2.2, and continuous in Figure 2.3. The active-date approach defined shorter active attempt durations compared to both the single question and the study gold standard date approach. Of the 867 women, 688 (79%) indicated that they "actively" started trying to conceive at some point during the period where they were at risk for pregnancy. The Pearson's correlation between the active-date approach compared with the date-based approach was 0.80. Using the active approach as the gold standard and the classic 12-month cutoff for subfertility, the sensitivity was 100% and the specificity was 24.4%, with 90% of cases correctly classified as infertile by the date approach. Sensitivity and specificity for all questions can be seen in supplemental tables 2.4-2.6. A total of 13.3% of women would be identified as not yet having met the cutoff for subfertility (<12 months) using the active date approach compared to the date-based approach.

To ensure that there was no systematic errors occurring due to intervening breaks

in attempts, we conducted a sensitivity analysis limited to longest attempts that were also first attempts. Eighty-two percent of single longest reported attempts were first attempts. The multinomial logistic regression had similar findings. The correlation between the date-approach and the single improved slightly (0.75) when limiting to first attempts but not significantly.

2.5 Discussion

We found that misestimation of longest single attempt duration occurred frequently when information was solicited using the common single question approach. Only a third (34%) of women accurately reported their longest attempt duration based on this single question when compared to information obtained using the date-based approach (+/- 3 months), while 37% of women overestimated and 29% of women underestimated their TARP using the single question approach. Women who *overestimated* their longest attempt with the single question approach were older when their first attempt started, had higher BMIs, and had longer time intervals between their first attempt and the time of the interview. Women who *underestimated* their TARP were older when their first attempt started, had lower educational attainment, and had a longer time interval between the start of their first attempt and the date of the interview. The risk of misestimation was significantly lower for women who had experienced a pregnancy (with or without live birth). This may be due in part to an isolation effect and the fact that they have a specific event to link the end of their pregnancy attempt. The sensitivity and specificity of the single question for capturing a person who had been trying for 24 months was good with over 90% being correctly identified as infertile using the 24-

month cutoff.

A strength of this study is the population studied, which included women with primary subfertility recruited through fertility clinics *in addition* to women recruited through population-based sampling. The design of this study excluded women with self-reported attempt durations of less than 1 year (based on a single question approach) and therefore is not generalizable to women who do not self-identify as having been at risk for pregnancy for less than 1 year.

There are a number of limitations of this study. It is retrospective and may be subject to recall bias. There may have also been some "learning" effect of being asked to report attempt durations multiple times over the course of the study; however, we used a calculated duration from the date-approach that we did not report back to the woman, and this may have attenuated the potential for attention bias. We believe the date-based approach used during the in-depth phone interview was the best measure available in this study, as trained study staff checked for chronology of events and were able to answer any questions that the participant may have had about what constituted the beginning and end of a discrete attempt. In absence of prospective study, however, we cannot say with certainty which of these approaches elicits the "correct" response. Still, the variability in responses to the three question approaches calls into question research findings or diagnoses that are based on just one of the three measures. Future research should explore differences in reporting of biological TARP and "active" behavioral time trying to conceive in a prospective manner in order to better understand the relationship between behaviors and attitudes toward pregnancy in infertile populations without telescoping effect or potential for recall bias.

The study of fertility and attempt duration is fraught with subjectivity. This study describes differences in retrospective measures of biological time at risk for pregnancy and reports of intentional pregnancy attempt durations obtain through different questioning approaches. We believe these findings highlight the value of taking a detailed attempt history using a date-based approach. The finding that women who experienced a pregnancy (regardless of live birth) were better at recalling attempt duration supports the use of a life event history framework.[14] The findings of this research also caution against assuming that biological TARP is equivalent to what is commonly referred to as "trying to conceive," which is imbued with intentionality, or that either of these measures can be determined using a single question. A variety of issues may affect how attempt duration is reported and the way in which the question regarding attempt duration is asked affects the answer. Additionally, in 2013, The Practice Committee of the American Society for Reproductive Medicine updated the definition of subfertility to include the phrase "12 months or more of **appropriately timed** unprotected intercourse or therapeutic donor insemination." This should be incorporated into questions assessing pregnancy attempt duration. Variations can cause bias in self-reports of time trying to conceive, skew fertility prognosis, and alter treatment plans. The percent of women who had yet to reach the WHO recommended 24-month threshold increased from the single question approach to the date-based approach (and increased even further when using the active attempt approach). Although unavailable in the current dataset this is likely to be the case for the 12-month cutoff as well. Physicians, in primary care and specialty settings, should avoid the use of a single question when assessing how long a couple has been having regular unprotected intercourse. Detailed

attempt histories should be used to capture a more accurate and complete picture of "time trying to conceive," including reports of the number of cycles using "fertility focused intercourse." Providers should also understand the potential impact of inaccurate pregnancy attempt reporting on patient treatment recommendations, which can unnecessarily increase patient's risk for undergoing potentially unnecessary treatments, which increase costs and may put them at risk for adverse perinatal outcomes.

Table 2.1 Participant characteristics by accuracy of reporting attempt duration by single question, as compared to date approach (N = 867)

	Single question >3mo UNDER date approach		Single question accurate (within 3 mo.)		Single question >3mo OVER date approach		P-value
	N	Row%	N	Row%	N	Row%	
Recruitment Site							
Clinic	146	34%	129	30%	158	36%	0.002
Population	103	24%	168	39%	163	38%	
Age at first attempt							
≤25	146	28%	192	37%	185	35%	0.223
26-30	53	24%	79	36%	85	39%	
31+	22	40%	16	29%	17	31%	
Age at Index							
18-25	64	21%	134	44%	104	34%	0.000
26-30	77	27%	103	36%	110	38%	
31+	80	39%	50	25%	74	36%	
BMI Category							
Underweight	4	19%	11	52%	6	29%	0.007
Normal	91	24%	147	39%	141	37%	
Overweight	62	31%	65	32%	75	37%	
Obese	66	34%	46	24%	80	42%	
Annual Income							
Less than $50,000	65	25%	102	39%	95	36%	0.370
50,000-$99,999	136	30%	157	34%	165	36%	
Over $100,000	30	27%	34	31%	47	42%	
Education Level							
Less than college grad	98	32%	90	29%	122	39%	0.045
College grad or more	149	27%	207	37%	199	36%	
Race/Ethnicity							
White, Non-Hispanic	227	28%	282	35%	306	38%	0.081
Hispanic, Other Non-White	22	42%	15	29%	15	29%	
Religion							
Non-LDS	71	35%	51	25%	83	40%	0.004
Latter-Day Saint	178	27%	246	37%	238	36%	
Insurance							
None or unsure	187	29%	222	34%	246	38%	0.806
Some insurance coverage for Dx or Tx	62	29%	75	36%	74	35%	
Highest attempt outcome							
Live birth, multiple	22	24%	27	29%	43	47%	0.000
Live birth, single	80	20%	154	39%	166	42%	
No pregnancy	139	43%	97	30%	90	28%	
Pregnancy, no live birth	8	16%	19	39%	22	45%	
Time between start of 1st attempt and interview							
<3years	9	12%	37	49%	29	39%	0.000
3-<6years	58	22%	117	44%	92	34%	
6-<10year	114	31%	118	32%	138	37%	
10 years +	68	44%	25	16%	61	40%	
Used Records							
No	128	28%	167	36%	165	36%	0.138
Yes	116	29%	130	33%	150	38%	
Perceived Subfertility							
No	27	28%	35	36%	35	36%	0.923
Yes	222	29%	262	34%	285	37%	
Most Invasive Tx							
None	32	24%	50	38%	51	38%	0.002
Alternative	13	42%	11	35%	7	23%	
Drugs	46	26%	67	38%	63	36%	
AI	52	25%	89	42%	69	33%	
IVF	106	33%	80	25%	131	41%	
Total	**249**	**29%**	**297**	**34%**	**321**	**37%**	

Table 2.2 Unadjusted Relative Risk Ratios for associations between misestimating attempt duration by more than 3 months using the single question compared to the date approach.

Exposure	Overestimating >3months [95% CI]	Underestimating >3months [95% CI]
Recruitment Site		
Clinic	1.26 [0.92, 1.73]	1.85 [1.31, 2.60]
Population	1.00 [Reference]	1.00 [Reference]
Age at first attempt*	1.00 [0.97, 1.05]	1.00 [0.96, 1.05]
BMI Category		
Underweight/Normal	1.00 [Reference]	1.00 [Reference]
Overweight/Obese	**1.50 [1.08, 2.09]**	**1.92 [1.34, 2.75]**
Annual Income		
Less than $50,000	1.00 [Reference]	1.00 [Reference]
$50,000-$99,999	1.13 [0.79, 160]	1.36 [0.92, 2.00]
Over $100,000	1.48 [0.88,2.50]	1.38 [0.77,2.48]
Education Level		
Less than college grad	1.00 [Reference]	1.00 [Reference]
College grad or more	**0.71 [0.51, 0.99]**	**0.66 [0.46, 0.94]**
Race/Ethnicity		
White, Non-Hispanic	1.00 [Reference]	1.00 [Reference]
Hispanic, Other Non-White	0.92 [0.44, 1.92]	1.82 [0.92, 3.59]
Religion		
Non-LDS	1.00 [Reference]	1.00 [Reference]
Latter-Day Saint	**0.59 [0.40, 0.88]**	**0.52 [0.35, 0.78]**
Insurance Coverage of Dx or Tx		
None or unsure	1.00 [Reference]	1.00 [Reference]
Some ins. Coverage	0.89 [0.61, 1.28]	0.98 [0.67, 1.44]
Longest attempt outcome		
No pregnancy	1.00 [Reference]	1.00 [Reference]
Pregnancy, no live birth	1.06 [0.61, 1.83]	**0.38 [0.20, 0.73]**
Pregnancy, Live birth	0.75 [0.54, 1.05]	**0.25 [0.17, 0.36]**
Time between start of 1st attempt and interview*	**1.01 [1.00, 1.02]**	**1.02 [1.01, 1.02]**
Most Invasive Tx		
None	1.00 [Reference]	1.00 [Reference]
Alternative	0.62 [0.22, 1.74]	1.84 [0.73, 4.62]
Drugs	0.92 [0.54, 1.55]	1.07 [0.60, 1.92]
IUI	0.76 [0.46, 1.25]	0.91 [0.52, 1.60]
IVF	1.60 [0.99, 2.59]	**2.07 [1.22, 3.52]**

*Continuous variables

Table 2.3 Multinomial logistic regression of over or under estimation of duration from single question compared to gold standard.

	Model 1 Adjusted		Model 2 Adjusted		Model 3 Adjusted RR	
Exposure	OVER [95% CI]	UNDER [95% CI]	OVER [95% CI]	UNDER [95% CI]	OVER [95% CI]	UNDER [95% CI]
Recruitment Site						
Clinic	0.82 [0.56, 1.19]	1.13 [0.74, 1.72]	0.86 [0.59, 1.26]	1.13 [0.74, 1.76]	0.85 [0.56, 1.27]	1.21 [0.78, 1.95]
Population	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Age at Index 1st attempt (years)	**1.04 [1.00, 2.04]**	**1.88 [1.27, 2.79]**	1.04 [0.98, 1.09]	1.04 [0.99, 1.11]	1.03 [0.98, 1.09]	1.04 [0.98,1.10]
BMI Category						
Underweight/Normal	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Overweight/Obese	**1.44 [1.01,2.05]**	1.26 [0.83, 1.89]	1.41 [0.99, 2.02]	**1.78 [1.18,2.68]**	**1.47 [1.02, 2.13]**	**1.89 [1.24, 2.88]**
Education Level						
Less than college grad	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
College grad or more	**0.64 [0.43, 0.93]**	**0.57 [0.37, 0.87]**	**0.65 [0.44, 0.97]**	0.67 [0.43, 1.05]	**0.66 [0.44, 0.98]**	0.66 [0.42, 1.04]
Religion						
Non-LDS	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Latter-Day Saint	0.68 [0.43, 1.07]	0.68 [0.42, 1.11]	0.74 [0.47, 1.16]	0.76 [0.46, 1.26]	0.73 [0.47, 1.17]	0.78 [0.47, 1.31]
Months between first attempt and Interview Continuous	**1.01 [1.00, 1.02]**	**1.01 [1.00, 1.02]**	**1.01 [1.01, 1.02]**	**1.01 [1.01, 1.02]**	**1.01 [1.00, 1.02]**	**1.01 [1.01, 1.02]**
Ultimate reproductive outcome						
No pregnancy			1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Pregnancy, no live birth			0.96 [0.53, 1.75]	**0.30 [0.14, 0.66]**	0.98 [0.53, 1.81]	**0.32 [0.14, 0.67]**
Pregnancy, live birth			0.70 [0.48, 1.02]	**0.23 [0.15, 0.36]**	**0.67 [0.45, 0.98]**	**0.22 [0.14, 0.35]**
Most invasive fertility treatment						
None					1.00 [Reference]	1.00 [Reference]
Alternative only					0.49 [0.16, 1.52]	1.34 [0.47, 3.80]
Drugs only					0.79 [0.43, 1.43]	0.61 [0.30, 1.23]
Intrauterine insemination					0.58 [0.32, 1.07]	0.50 [0.25, 1.03]
In vitro fertilization					1.15 [0.63, 2.08]	1.00 [0.50, 2.00]

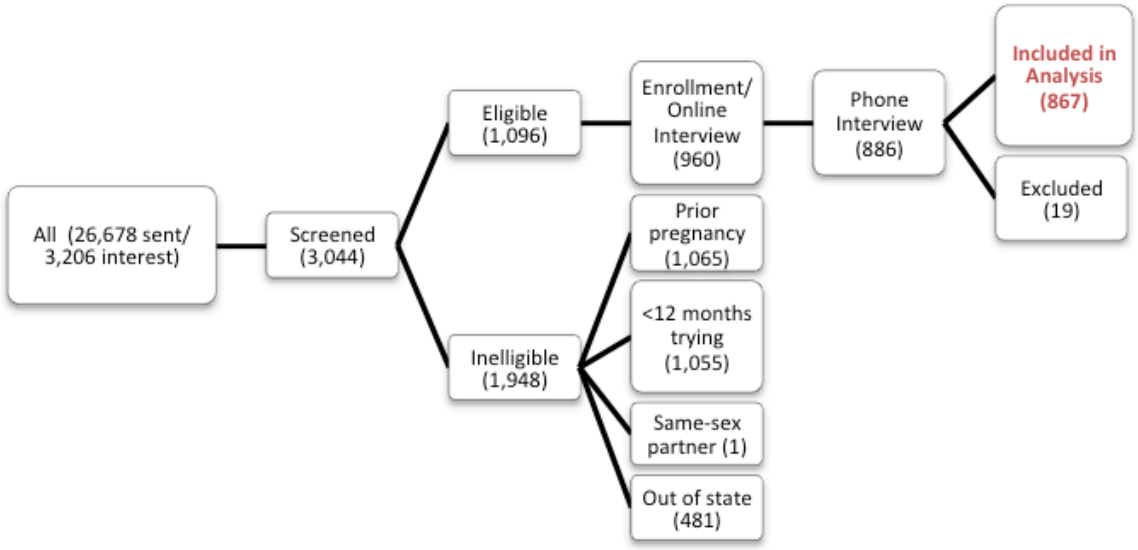

Figure 2.1 TARP participant flowchart

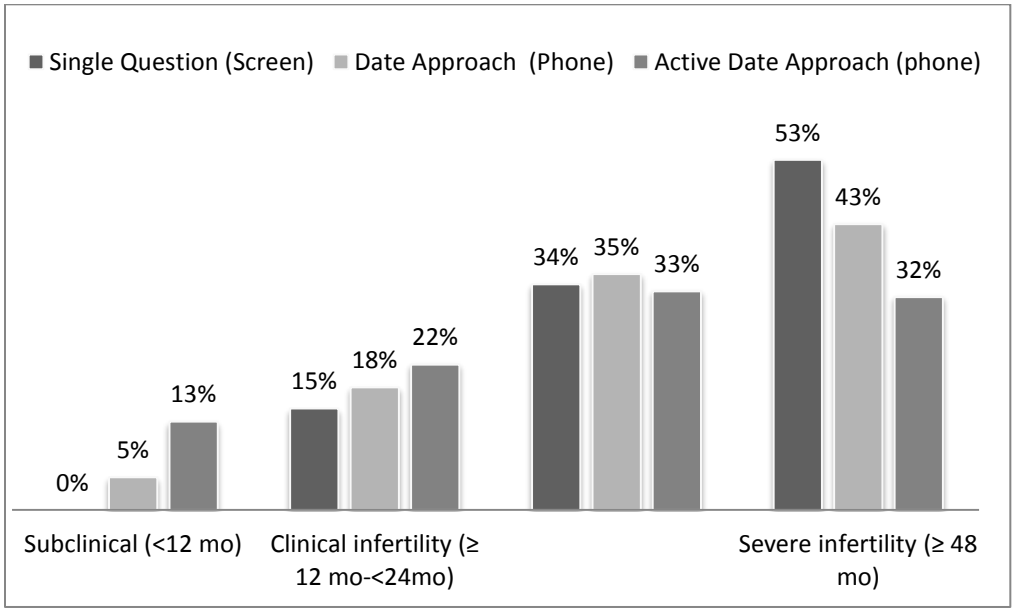

Figure 2.2 Distribution of longest TARP

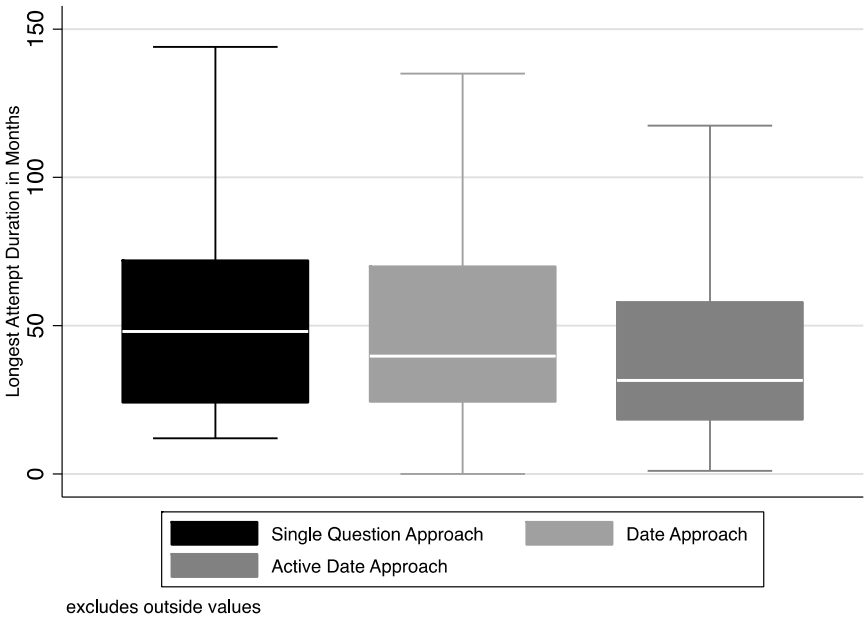

Figure 2.3 Distribution of longest reported duration between date approach and single question approach and active-date approach (in months)

2.6 Reference

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CHAPTER 3

BEHAVIORAL, NONMEDICAL, AND MEDICAL INTERVENTIONS REPORTED BY WOMEN WITH PRIMARY SUBFERTILITY

3.1 Abstract

The objective of this chapter is to describe the use of behavioral, nonmedical, and medical interventions reported by women who experienced primary infertility. A retrospective cohort study of women who experienced primary infertility in Utah between 2000 and 2009 was developed. Participants were recruited from specialty reproductive endocrinology clinics and the general population. Women were asked about the use of interventions used to enhance fertility, either on their own or by recommendation of a doctor. Interventions included fertility-focused intercourse (by basal body temperature, cervical fluid, urine LH, and/or counting days); behavioral changes (weight loss, adherence to fertility diets); complementary and alternative medicine (CAM: vitamins, herbs, and/or acupuncture); and medical treatments (ovulation stimulation drugs (OS), intrauterine insemination (IUI), and/or assisted reproductive technologies (ART) including in-vitro fertilization (IVF) with or without intra-cytoplasmic sperm injections (ICSI)). We also assessed male partner treatments in a subgroup of participants.

The mean number of total interventions used by women was 3.4, range 0 to 8 (maximum possible 9). Nearly all (94%) women (n = 867) used fertility-focused

intercourse, most with multiple indicators of fertility. At least one type of CAM was used by 33% of women, and over 80% reported use of one or more medical treatments. Compared to women recruited from specialty infertility clinics, women from the general population were less likely to use any type of medical treatment, but equally likely to use nonmedical interventions.

Women commonly use a mix of medical and nonmedical interventions while trying to conceive. Both primary care clinicians and fertility specialists should assume that nearly all their patients are using some type of nonmedical intervention and should take a full history that includes assessment of behavioral changes and interventions in complementary and alternative medicine.

3.2 Introduction

The majority of infertility research occurs in clinical settings where patients are actively seeking medical diagnosis and treatment. However, little is known regarding the use of nonmedical interventions intended to increase chances of conception used by women with extended pregnancy attempts. In addition, the medical and nonmedical interventions used by women from the general population have not been described previously. Research defining infertility as regular unprotected intercourse without a resulting conception after 12 months or more finds the prevalence of infertility among women currently trying to become pregnant to be around 15% in the United States.[1] For women who have never been pregnant before, this condition is referred to as primary infertility or subfertility.

Women who have difficulty conceiving commonly seek medical diagnosis; about

half of women who suffer from subfertility seek medical treatment from a healthcare provider.[2] About one in 10 women in the United States receive some type of medical fertility service.[3] Medical interventions to treat infertility include ovulation stimulation medications (OS), intrauterine insemination (IUI), and assisted reproductive technologies (ART) including in-vitro fertilization (IVF).[4] The most recent clinic surveillance of ART from 2012 reports close to 200,000 IVF cycles resulting in 51,267 live births in the United States.[5] Births conceived during IVF cycles comprise over 1% of all births in the United States, and another 1% of live births result from IUI cycles.[6] Estimating the use of ovulation enhancing drugs is more difficult as both primary care and specialty providers manage infertility using these medications, and there is no formal reporting system. However, it is estimated that OS accounts for up to 6% of the births in the United States.[7]

In addition to medical treatments, couples that are having difficulty conceiving may explore nonmedical or behavioral interventions. Some of these interventions have strong data supporting their effectiveness, while others need more research. Data exist to support the use of fertility-focused intercourse to increase per-cycle pregnancy rates in couples without evidence of infertility.[8, 9] Fertility-focused intercourse approaches include tracking basal body temperatures (BBT), using luteinizing hormone (LH) test kits, monitoring cervical mucus (CM), and counting cycle days using a simple calendar method to predict fertile days. These approaches are intended to optimize natural fertility rather than treat an underlying condition. Monitoring menstrual cycles using the biosymptom approaches can be useful in determining underlying conditions contributing to a couples' difficulty conceiving.[10] However, it is critical for individuals attempting to conceive to use these methods correctly.[11] There is potential to inadvertently practice

pregnancy prevention or to misinterpret observations if these methods are poorly understood.

Other nonmedical interventions include loosing or gaining weight to achieve a "normal" or healthy body mass index (BMI) and to improve overall health and reproductive capacity. The American Society for Reproductive Medicine (ASRM) estimates that about 12% of infertility cases are due to the female partner weighing too little or too much.[12] BMI that is too high (>25kg/m^2) or too low (<19 kg/m^2) can affect ovulation and cycle length.[13]

Although different from weight management interventions, another behavioral change that is sometimes reported is the use of "fertility diets." Fertility diets typically recommend changing micronutrient profiles to enhance fertility. A growing body of research substantiates these interventions.[14] Any Google search for "foods to enhance fertility," or "fertility diets" will provide ample reading pointing to a mixture of pseudoscientific claims as well as claims based on scientific research on food and diet changes that can improve a couple's chance of conceiving.

Couples having difficulty conceiving may turn to a variety of interventions or treatments that are outside the realm of conventional medicine. These approaches are sometimes referred to as complementary and alternative medicines (CAM). Although there are a many CAM approaches that have been explored, some of the more commonly reported fertility-related interventions include the use of vitamins, herbs, and/or acupuncture.[15, 16]

Vitamins are generally considered a more western approach to health than herbs or acupuncture, but use of vitamin supplements is often considered CAM, as they are not

routinely evaluated in clinical trials. Common vitamins that are used to enhance fertility include B-complex, vitamin C, vitamin E, and folic acid for women and L-carnitine, vitamin C, vitamin E, vitamin A, selenium, zinc, and beta-carotene for men. Studies yield mixed findings on the efficacy of vitamin supplements for the treatment of infertility or enhancement of fertility.[17-20]

The prevalence of use of medicinal herbs varies greatly between cultures and geographic regions of the world. A recent 18-month prospective cohort study of infertile couples in the United States found that about 17% of couples report using herbs to enhance their fertility while undergoing ART.[16] Herbs used in products that are marketed to enhance fertility include vitex, red clover, Siberian ginseng, ginko biloba, maca root, and Asian ginseng.[21] There has been some research of varying quality on herbal supplements and their effect on fertility.[22-24]

Acupuncture is a traditional Chinese medicine practice that involves placing needles in the skin to stimulate certain points on the body.[25-30] Smith et al. (2010) found that 22% of infertile couples in their study used acupuncture over the course of 18 months.[16] The effects of acupuncture on infertility have been inconclusive. Some evidence suggests that acupuncture provided in conjuncture with embryo transfer may increase rates of pregnancy and live birth[31]; however, a Cochrane review found no evidence to support acupuncture and went further to recommend against acupunctures use with IVF during egg retrieval or implantation.[25] A 2013 meta-analysis of randomized trials of acupuncture and IVF embryo transfer found no pooled benefit for providing acupuncture with IVF embryo transfer.[27]

Modern technology, mommy blogs, and social media have provided couples

wishing to conceive with a plethora of unsubstantiated information on ways to enhance fertility. The purpose of this analysis is to describe the use of various behavioral, nonmedical and medical interventions among a cohort of women from the general population and specialty infertility clinics with a history of primary infertility. We also examine the use of combinations of interventions, including interventions utilized by male partners. Pregnancies that occurred during the cycles when these approaches were utilized are also reported.

3.3 Methods

The Fertility Experiences Study (FES) is a retrospective cohort study conducted at the University of Utah between April 2010 and September 2012. The FES cohort was developed with the intention of identifying women with primary infertility that may or may not have received clinical diagnosis or medical treatment. Women were recruited from infertility clinics as well as the general population. The clinic-based cohort was recruited from two specialty fertility clinics in Utah. For clinic recruitment, study invitations were mailed to all women who had an initial infertility visit during the index years of 2004 and 2008. The population-based cohort was identified by the Utah Population Database (UPDB) based on a linkage between state marriage, birth, and fetal death records. Couples with a marriage record and no record of a live birth or fetal birth within 2 years of marriage were considered eligible for screening. Recruitment of the population-based cohort was facilitated by the Resource for Genetic and Epidemiologic Research (RGE) at the University of Utah to protect the identity of women who were not interested in enrolling. RGE mailed invitation letters and followed up potential

participants to inform them of the study and determine if they would be willing to be contacted by study staff for eligibility screening. Interested individuals from both the general population and two specialty clinics were screened for eligibility using the same criteria. The parallel clinic-based and population-based cohorts consist of women residing in the State of Utah with a history of primary infertility (i.e., trying to conceive for at least 1 year, with no prior pregnancies) as of a specified index date between 2004 and 2008. Women determined to be eligible were then invited to complete a self-administered online (or paper) questionnaire. Upon completion of the questionnaire, trained study staff completed an in depth phone interview. Participants received a $10 gift card and a handwritten thank you note as compensation for their time. The development of the FES cohort and data collection methodology has been described in detail elsewhere (Cite methods paper). The University of Utah Institutional Review Board approved this study.

During the in-depth phone interview study staff read the line "I will now ask about things you may have done to enhance fertility during this particular attempt to conceive, either on recommendation of a doctor or on your own…. In order to conceive, have you done any of the following: [Intervention], during this particular attempt? If so was it used during the month of conception of pregnancy?"

Descriptive analysis was performed to examine characteristics of women who utilized various interventions with the specified goal of increasing their fertility. We created treatment categories by combing interventions. Fertility-focus intercourse includes BBT, urine LH tests, counting days, and monitoring CM; weight loss and the use of "fertility diets" were grouped as behavioral interventions; CAM measures included

vitamins, herbs, and acupuncture; and medical treatments included OS, IUI, and ART. Mutually exclusive categories of interventions (other than behavior changes and fertility-focused intercourse) were created to identify the most invasive treatments/interventions used for women who used a variety of approaches. Women who used only fertility focused intercourse, fertility diets, or weight loss were categorized as using no treatments. Women who used vitamins, herbs, or acupuncture without medical treatments and with or without behavioral changes were categorized as using CAM. Medical treatments were grouped as follows: women who had used OS (without IUI or ART), women who used IUI (with or without OS and/or CAM/behavioral changes), and women who used ART (with or without any other interventions). A subset of participants was also asked about interventions that their male partners used during their pregnancy attempts and the prevalence of partner-focused interventions was documented. Chi-square tests were used to evaluate differences in the frequency of use of each intervention, stratified by participant characteristics. Combinations of treatments ever used are also described. Multivariable logistic regression models were assessed to assess for characteristics that made women more likely to use a particular intervention.

Covariates considered were recruitment cohort (clinic vs. population), age at start of first pregnancy attempt, education level, religious affiliation (specifically affiliation with the Church of Jesus Christ of Latter-Day Saints), income level, race/ethnicity, longest pregnancy attempt duration over 24 months, pregnancy outcomes, and other treatments used.

3.4 Results

A total of 960 women enrolled in FES; 501 women were recruited from the population and 459 women were recruited from infertility clinics. Most women enrolled (92%) completed all three parts of the study including the screening questionnaire, the self-administered questionnaire, and the phone interview. Nineteen women with missing pregnancy attempt data were dropped from the analysis: four women had dates that were improperly formatted and 15 women had missing attempt end dates but were not "still trying to conceive" at the time of the interview. A total of 867 women were retained for the analysis. Half of the women were recruited from fertility clinics, and half were recruited from the general population. Women recruited from the general population were younger on average and had lower incomes than infertility clinic patients. Less than half of the women were asked about insurance coverage for fertility but of women who were asked, 75% indicated they had some insurance coverage for diagnostics or treatment in both cohorts ($p = 0.78$). Women recruited from the clinic reported having longer pregnancy attempt duration and were more likely to use IUI or ART than women recruited from the population cohort (Table 3.1).

Two thirds of women eventually had a pregnancy; approximately two-thirds ($n = 541$) had at least one pregnancy, 91% ($n = 492$) of these pregnancies resulted in a live birth, and 9% ($n = 49$) had at least one pregnancy but had never had a live birth (this includes 14 women who were currently pregnant at the time of the phone interview for whom pregnancy outcomes are unknown). Women recruited from the specialty clinics used different types of treatments than women recruited from the general population; however, there was no difference in the proportion of women achieving at least one

pregnancy in the two groups (64% versus 63%; p = 0.76). There were significantly more clinic recruited women who had at least one pregnancy ending in a multiple gestation birth compared to women recruited from the population (23% versus 11%; p-value < 0.01).

The most commonly used intervention was fertility-focused intercourse, which was reported by 94% of participants. Of women who had a pregnancy, 60% indicated they were using some fertility-focused method during the cycle of conception. Other behavioral interventions asked about were weight loss and the use of fertility diets, and 35% of women reported that they had ever used these behavioral interventions to enhance their fertility, whereas 9% were using these methods during the month of conception. Complementary and alternative interventions were reported by a third (33%) of women (Table 3.2). Of women who were using CAM, 20% of vitamin users were using them during the month of conception, 11% of herb users were using the herbs during the month of conception, and 9% of acupuncture users were using it during the month of conception.

Medical treatment was common in both clinic and population cohort recruited women. Eight out of 10 women in the study reported using OS as some point in their attempt history, and 35% of women whom ultimately had a pregnancy in the study conceived during an OS cycle. Half of the women reported using IUI during their pregnancy attempts and 35% conceived in an IUI cycle. ART was the least frequently reported medical intervention reported, but about 38% of women who had pregnancies achieved them during an ART cycles (Figure 3.1).

During the pregnancy attempt history, women frequently reported using more

than one method to enhance their fertility (Table 3.3). Only 3% of women reported not using anything during their pregnancy attempt history (fertility focused intercourse, weight loss, fertility diets, vitamins, herbs, acupuncture, OS, IUI, ART). The average number of interventions used was 3.4, but ranged from 0 to 8 (potential max is 9). Overlap in interventions may indicate sequential or concurrent use. Nearly all (99%) individuals who had used any intervention, CAM, OS, IUI, or ART, also used a fertility-focused intercourse approach, whereas only 78% of women who never used any intervention were using any of these methods.

Use of fertility diets were not as common as other interventions in this cohort; only 16% indicated they had ever used a fertility diet. Weight loss was commonly reported among all women (29%). Women who were overweight or obese at the time of the interview more frequently (42%) reported weight loss as something they had ever tried. Individuals who had less than college education also more frequently reported weight loss as an intervention used. Women with no insurance coverage for treatment or diagnosis less frequently reported using fertility diets. Women who used CAM as their highest treatment more frequently reported using fertility diets followed by women who had used ART. Women who had used OS were the most likely to report weight loss out of the mutually exclusive treatment categories. There was a distinction made between fertility diets and weigh loss. Only about 10% of women reported using both "fertility diets" and weight loss during their pregnancy attempt histories.

A third of women (n = 287) reported using CAM in at least one attempt, but only 4% (n = 31) reported CAM as their most invasive treatment. When combining all CAM, women who had no insurance coverage for any fertility treatment or diagnosis

reported less use of CAM. However, there were other differences between characteristics when looking at vitamins, herbs, and acupuncture separately. More frequent use of vitamins were reported by women who were underweight or normal BMI compared to overweight or obese women, those who had incomes over $100,000 compared to women who reported lower incomes, and those who never had a pregnancy. Individuals from the clinic-based cohort compared to the population-based cohort and those who had never had a pregnancy more frequently reported use of herbs. Acupuncture was more frequently used by women who were 31 years of age or older than younger women, women who were underweight, or normal BMIs at the time of the interview.

There was a high rate of medical treatment used in this population, with 81% (n = 703) reporting some type of medical treatment during their attempt to conceive. Close to three quarters of the women in FES reported the use of ovulation enhancing drugs during at least one attempt (n = 629). Over two-thirds of these women also had more invasive treatments. Four-hundred and thirty-six women (50%) used IUI during at least one attempt; close to half of these women who used IUI also used IVF (n = 317). There were significantly more women reporting all three treatments among those recruited from the clinics. Both IUI and ART treatments were most frequently reported by women who were underweight/normal BMI, had annual incomes over $100,000, and had some insurance coverage for infertility diagnosis or treatment. ART was also most frequently reported by women who were over 31 years of age at the beginning of their first attempt. Of women who used some medical treatment, only 28% of individuals use a single medical intervention. Many women (14%) reported using ovulation enhancing drugs, IUI, and ART consecutively during a single pregnancy attempt, though not during the same cycle.

Overall, only 15% (n = 133) of women in this cohort did not use any medical interventions to enhance their fertility, this may have been indicative of less severe fertility as these women has significantly shorter pregnancy attempt duration (50% less than 24-months) compared to women who used treatment and had similar rates of pregnancy (60%).

A subgroup of 363 women were asked specifically about things their male partners may have done to enhance fertility during attempts to conceive. The most common intervention used by male partners was weight loss (6%). Women reported that male partners also used fertility diets (5%), vitamins (6%), herbs (5%), acupuncture (2%), medications such as Clomid (3%), and hormonal treatments (3%). Women who were overweight or obese also more frequently reported male partner weight loss. About 5% of women who were asked reported that both they and their partner had lost weight to try to enhance their fertility, while 4% reported both partners had used "fertility diets." Only three (<1%) women reported that they and their partner used both fertility diets and weight loss as a way to enhance their fertility (Table 3.4).

When adjusting for recruitment cohort, age at first attempt, BMI category, income, education, ethnicity, pregnancy, and longest attempt duration, women who self identify as LDS were 2.1 times as likely to practice fertility focused intercourse than non-LDS women. Women who used CAM were 4.43 times as likely [95% CI 1.27-15.41] as women who did not used any CAM to incorporate fertility-focused intercourse into their attempts. Women who ever used OS or IUI were also more likely to report fertility-focused intercourse [aOR 3.2; 95% CI 1.46-7.06] and [aOR 7.46; 95% CI 1.61-34.66], respectively. Multivariable regression controlling for the same aforementioned

confounders found LDS women less likely than non-LDS women to use CAM [aOR 0.64; 95% CI 0.42-0.98]. Women who reported ever using fertility focused intercourse were 4.5 times more likely than nonusers to report CAM interventions. IUI users were 1.5 times more likely than non-IUI users, and ART users were 2.5 times more likely than non-ART users to report ever using CAM (Table 3.5). When collapsing all medical treatment into a single category (medical treatment vs. no medical treatment) women from the clinic-based cohort were 9.4 times more likely to report ever using a medical treatment, LDS women were 2 times more likely to use medical treatments than non-LDS women, and women who had attempts lasting longer than 24 months were also more likely to use any medical treatment compared to women who had shorter attempts, when controlling for age, BMI, income, education, and ethnicity (Table 3.6).

Separate multivariable logistic regression was done to assess the association of interventions with each other (Table 3.7). When controlling for recruitment site, age, BMI, income, education, race/ethnicity, and religion, women who used medical interventions were 5.2 times as likely to use fertility focused intercourse than women who did not use any medical treatments. They were also 1.94 times as likely to use some type of CAM during their pregnancy attempts. Women who had longest attempts of longer than 24 months were about twice as likely to use CAM and/or medical treatments than women who had tried for shorter durations (Table 3.7).

3.5 Discussion

In this study, nearly all participants (94%) engaged in fertility-focused intercourse methods during at least one pregnancy attempt. A third of women (35%) either lost

weight or changed their diet with the intention of enhancing their fertility. A third of women (n = 287) also reported using CAM in at least one attempt but only 4% (n = 31) reported CAM as their most invasive treatment. There was a high rate of medical treatment used in this population, with 81% (n = 703) reporting some type of medical treatment, including OS, IUI, and/or ART. Overall, only 15% (n = 133) of women in this cohort never used any intervention to enhance their fertility. In the subgroup of women who were asked about things their partner might have done to enhance fertility there were few that reported any male partner interventions, suggesting that men are not as engaged in behavioral modifications or self-care interventions as their female counterparts. Given that in 40% of infertile couples, the underlying cause of infertility involves some male factor, this is an area of research that should be explored further as there may be potential to increase a couples natural fertility by involving men in healthy behavioral modifications that may benefit sperm quality or motility.[32] A major limitation of the study is that the dates of interventions were not collected; thus, we are unable to account for order of interventions used, exact duration of intervention use, or concurrent use of interventions if participants indicated their use during a single pregnancy attempt. We were only able to identify concurrent use of interventions if they were used in a cycle resulting in a conception.

The design of the FES is unique in that it explores interventions by couples with a history of primary infertility recruited through fertility clinics as well as women who were recruited through a population-based sample. This allows us to examine how women may attempt to enhance their fertility outside of fertility clinics. The use of nonmedical interventions was common in both the clinic and population recruited cohort.

It is necessary for providers to complete a full intervention inventory in addition to medical history with patients at all clinical encounters. Having a more complete picture of the things that women are doing either on their own or with CAM practitioners or other medical providers can improve treatment precision. Providers need to acknowledge that more likely than not their patients are engaging in nonmedical interventions with the intention of enhancing their fertility, but without adequate counseling women may be using approaches that could have opposing effects on treatments. Women who have been trying for longer are also more likely to engage in more interventions and should be asked to report on the things they may have tried over the years. The use of an intervention checklist to assess what nonmedical interventions patients are using has the potential to create open communication between patients and specialty providers by removing stigma surrounding nonmedical CAM and ensuring that providers have the most complete clinical picture when treating individual cases. This may also be an opportunity to ensure that their long durations of "regular, unprotected intercourse" also included at least 12 cycles of appropriate fertility-focus intercourse. These interactions with patients who are struggling to conceive is an ideal opportunity to discuss preconception care including the use of prenatal vitamins and achieving a healthy prepregnancy weight.

Table 3.1 Demographic and reproductive characteristics of participants by source cohort (N = 867)

	Clinic		Population		Total		P-value
	N	%	N	%	N	%	
Total	433	49.9%	434	50.1%	867	100.0%	
Age at first attempt to conceive							
≤25	206	56.9%	317	73.2%	523	65.8%	**0.000**
26-30	110	30.4%	107	24.7%	217	27.3%	
31+	46	12.7%	9	2.1%	55	6.9%	
BMI Category							
Underweight	7	1.8%	14	3.5%	21	2.6%	0.238
Normal	200	50.4%	179	45.1%	379	47.7%	
Overweight	95	23.9%	107	27.0%	202	25.4%	
Obese	95	23.9%	97	24.4%	192	24.2%	
Annual Income							
Less than $50,000	105	25.4%	157	37.6%	262	31.5%	**0.000**
50,000-$99,999	232	56.2%	226	54.1%	458	55.1%	
Over $100,000	76	18.4%	35	8.4%	111	13.4%	
Education Level							
Less than college graduate	152	35.3%	158	36.4%	310	35.8%	0.727
College graduate or more	279	64.7%	276	63.6%	555	64.2%	
Race/Ethnicity							
White, Non-Hispanic	402	92.8%	413	95.2%	815	94.0%	0.150
Hispanic or other non-white	31	7.2%	21	4.8%	52	6.0%	
Religion							
Non-LDS	114	26.3%	91	21.0%	205	23.6%	0.063
Latter-Day Saint	319	73.7%	343	79.0%	662	76.4%	
Insurance coverage for fertility							
None or unsure	32	7.4%	59	13.6%	91	10.5%	**0.000**
Some coverage	100	23.1%	172	39.6%	272	31.4%	
Not asked	301	69.5%	203	46.8%	504	58.1%	
Longest attempt duration							
<12mo	6	1.4%	36	8.3%	42	4.8%	**0.000**
12-<24	68	15.7%	89	20.5%	157	18.1%	
24-<36	80	18.5%	85	19.6%	165	19.0%	
36-<48	78	18.0%	59	13.6%	137	15.8%	
48+	201	46.4%	165	38.0%	366	42.2%	
Fertility Outcome							
No Pregnancy	160	37.0%	166	38.3%	326	37.6%	0.496
Pregnancy, live birth	252	58.2%	240	55.3%	492	56.8%	
Pregnancy, no birth	21	4.9%	28	6.5%	49	5.7%	

Table 3.2 Fertility interventions used by participants' demographic and reproductive outcome

		Fertility Focused Intercourse	Behavioral Changes		Complementary-Alternative Medicine			Medical Treatment		
	Total	Any	Fertility Diet	Weight Loss	Vitamins	Herbs	Acupuncture	OS	IUI	ART
Total N (%)	**867**	94.3%	16.4%	28.6%	12.0%	17.1%	15.6%	72.5%	50.3%	36.6%
Recruitment Site	**867**									
Clinic	433	91.7%**	15.2%	27.3%	11.5%	20.1%*	16.6%	77.1%*	61.2%*	47.8%*
Population	434	82.9%**	15.9%	27.0%	12.4%	14.1%*	14.5%	58.5%*	33.6%*	21.0%*
Age at 1st attempt	**795**									
≤25	523	93.6%	17.9%	30.3%	12.4%	17.3%	14.5%*	71.1%	45.7%	32.7%*
26-30	217	92.6%	12.9%	24.4%	11.1%	14.3%	17.1%*	72.4%	52.1%	35.0%*
31+	55	92.7%	18.2%	18.2%	12.7%	16.4%	23.6%*	69.1%	54.5%	63.6%*
BMI Category	**794**									
Underweight/Normal	400	94.3%	15.3%	14.8%**	14.8%*	16.0%	17.8%*	71.8%	54.8%*	42.5%*
Overweight/ Obese	394	93.7%	17.3%	42.6%**	9.6%*	17.3%	12.4%*	74.6%	46.2%*	32.5%*
Annual Income	**831**									
Less than $50,000	262	92.4%	15.6%	32.8%	12.6%*	17.9%	13.0%	67.6%	40.1%*	28.2%*
50,000-$99,999	458	90.1%	14.4%	25.2%	9.9%*	16.5%	15.1%	71.3%	50.9%*	33.6%*
Over $100,000	111	93.7%	21.6%	27.9%	18.9%*	14.4%	18.0%	73.0%	61.3%*	59.5%*
Education Level	**865**									
Less than college grad	310	92.9%	17.1%	32.6%*	11.6%	18.7%	14.8%	73.2%	48.7%	32.9%
College grad or more	555	95.1%	16.0%	26.5%*	12.3%	16.2%	16.0%	72.3%	51.4%	38.4%
Race/Ethnicity	**867**									
White, Non-Hispanic	815	94.6%	16.3%	28.6%	11.9%	16.8%	15.2%	72.9%	50.3%	36.8%
Hispanic, Other Non-White	52	90.4%	17.3%	28.8%	13.5%	21.2%	21.2%	67.3%	50.0%	32.7%
Religion	**867**									
Non-LDS	205	91.7%	17.6%	29.3%	14.1%	17.6%	18.5%	69.3%	47.8%	35.6%
Latter-Day Saint	662	95.2%	16.0%	28.4%	11.3%	16.9%	14.7%	73.6%	51.1%	36.9%
Insurance coverage for fertility	**867**									
None or unsure	91	85.7%*	9.9%*	14.3%	11.0%	24.2%	47.3%*	28.6%*	33.0%*	23.1%*
Some coverage	272	95.2%*	12.9%*	25.0%	9.2%	23.9%	69.1%*	47.1%*	37.1%*	26.5%*
Not asked	504	95.4%*	19.4%*	33.1%	19.8%	39.7%	79.0%*	30.6%*	60.5%*	44.4%*
Longest attempt duration	**867**									
<24 months	199	90%**	14.1%	26.1%	6.5%**	7.0%**	15.6%	60.8%**	31.2%**	23.6%**
24 months or longer	668	95.7%**	17.1%	29.3%	13.6%**	20.1%**	15.6%	76.1%**	56.0%**	40.4%**

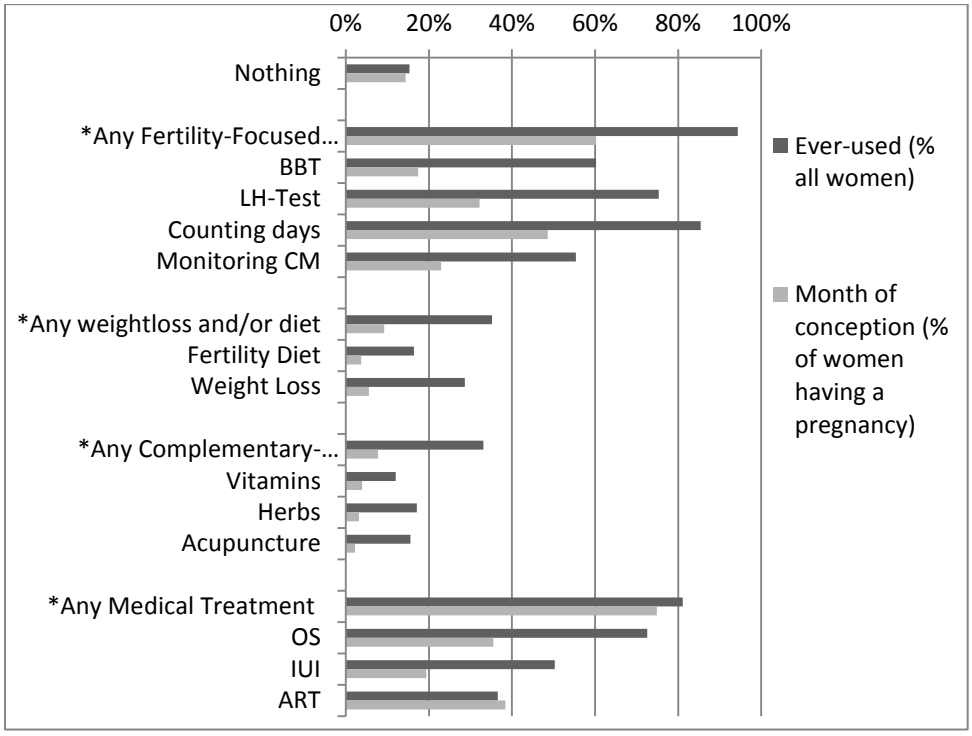

Figure 3.1 Use of all interventions ever and during the month of conception

Table 3.3 Overlap between fertility interventions ever used

	Fertility-focused intercourse				Diet and weight		Complementary & alternative medicine			Medical treatment		
	BBT	LH-Test	Monitoring CM	Counting days	Weight Loss	Fertility Diet	Vitamins	Herbs	Acupuncture	OS	IUI	ART
BBT		81%	65%	92%	31%	20%	15%	21%	19%	81%	57%	40%
LH-Test	65%		57%	93%	28%	16%	13%	20%	16%	80%	59%	37%
Monitoring CM	70%	83%		93%	33%	25%	15%	22%	24%	76%	58%	43%
Counting days	65%	82%	60%		29%	17%	13%	19%	17%	76%	53%	37%
Weight Loss	65%	74%	65%	88%		37%	16%	19%	30%	83%	57%	42%
Fertility Diet	74%	74%	86%	89%	64%		20%	23%	56%	86%	68%	61%
Vitamins	76%	82%	70%	90%	38%	28%		50%	24%	79%	55%	42%
Herbs	74%	86%	70%	95%	32%	22%	35%		26%	82%	58%	36%
Acupuncture	74%	77%	85%	92%	55%	59%	19%	28%		92%	79%	70%
OS	67%	83%	58%	90%	33%	19%	13%	19%	20%		65%	41%
IUI	68%	88%	63%	90%	33%	22%	13%	20%	24%	93%		52%
ART	67%	76%	64%	87%	32%	27%	14%	17%	30%	81%	71%	

Table 3.4 Two-way correlation of all fertility interventions ever used by female and male partners, N = 363

	Total N (%)	BBT	LH-Test	Monitoring CM	Timed	Weight Loss	Partner Weight loss	Fertility Diet	Pt. Fertility Diet	Supplement	Pt Supplement	Vitamins	Pt Vitamins	Herbs	Pt Herbs	Acupuncture	Pt Acupuncture*	Shots	Hormones	Pt Hormones	Drugs	Pt Drugs	IUI	ART	Other	% of Total
BBT	206	100%	81%	63%	89%	26%	8%	17%	6%	9%	6%	12%	8%	19%	8%	14%	3%	36%	54%	2%	75%	4%	43%	31%	29%	57%
LH-Test	258	64%	100%	59%	90%	23%	6%	12%	4%	6%	3%	10%	6%	16%	5%	10%	2%	33%	48%	2%	73%	3%	45%	27%	26%	71%
Monitoring CM	190	68%	79%	100 %	91%	20%	5%	16%	4%	8%	5%	11%	9%	18%	8%	13%	3%	32%	46%	3%	64%	3%	38%	28%	27%	52%
Timed	297	62%	78%	58%	100 %	23%	6%	13%	5%	7%	4%	9%	6%	16%	6%	11%	2%	30%	44%	3%	68%	4%	38%	26%	26%	82%
Weight Loss	81	65%	74%	47%	84%	100 %	22%	22%	9%	12%	2%	10%	6%	15%	2%	10%	2%	30%	51%	6%	74%	0%	33%	22%	20%	22%
Partner Weight loss	22	73%	68%	45%	86%	82%	100 %	23%	14%	23%	5%	23%	5%	18%	5%	9%	5%	32%	32%	9%	68%	0%	36%	23%	27%	6%
Fertility Diet	44	77%	73%	70%	91%	41%	11%	100%	34%	16%	9%	20%	9%	30%	18%	25%	7%	45%	61%	7%	70%	2%	36%	198%	34%	12%
Pt. Fertility Diet	17	76%	65%	47%	94%	41%	18%	88%	100%	12%	12%	18%	12%	24%	24%	35%	6%	53%	6%	71%	0%	0%	41%	41%	65%	5%
Supplement	23	78%	70%	70%	96%	43%	22%	30%	9%	100%	22%	26%	4%	35%	17%	17%	13%	39%	43%	9%	70%	0%	39%	39%	26%	6%
Pt Supplement	13	100%	69%	69%	92%	15%	8%	31%	15%	15%	100%	23%	15%	31%	46%	38%	15%	38%	62%	8%	69%	0%	38%	46%	46%	4%
Vitamins	32	78%	78%	66%	84%	25%	16%	28%	9%	19%	9%	100%	34%	44%	19%	34%	16%	34%	59%	3%	75%	3%	44%	41%	28%	9%
Pt Vitamins	20	80%	80%	90%	90%	25%	5%	20%	10%	5%	10%	55%	100%	30%	20%	35%	5%	30%	55%	0%	70%	5%	60%	50%	20%	6%
Herbs	53	75%	79%	66%	91%	23%	8%	25%	8%	26%	8%	26%	11%	100%	26%	30%	9%	30%	62%	0%	77%	6%	47%	30%	30%	15%
Pt Herbs	18	89%	78%	89%	94%	11%	6%	44%	22%	22%	33%	33%	22%	78%	100%	39%	17%	22%	67%	0%	61%	6%	50%	39%	39%	5%
Acupuncture	35	80%	74%	69%	97%	23%	6%	31%	17%	11%	14%	31%	20%	46%	20%	100%	17%	34%	66%	0%	86%	11%	40%	37%	29%	10%
Pt Acupuncture	7	100%	71%	86%	100 %	29%	14%	43%	14%	14%	43%	71%	14%	71%	43%	86%	100%	57%	71%	0%	100%	14%	43%	57%	29%	2%
Shots	109	69%	78%	55%	81%	22%	6%	18%	6%	8%	5%	10%	6%	15%	4%	11%	4%	100%	84%	6%	81%	5%	67%	74%	27%	30%
Hormones	154	72%	81%	56%	86%	27%	5%	18%	6%	6%	5%	12%	7%	21%	8%	15%	3%	60%	100%	3%	83%	4%	51%	51%	25%	42%
Pt Hormones	9	56%	56%	67%	100 %	56%	22%	33%	11%	22%	11%	0%	0%	0%	0%	0%	0%	67%	56%	100%	78%	22%	56%	44%	22%	2%
Drugs	231	67%	81%	52%	87%	26%	6%	13%	5%	7%	4%	10%	6%	18%	5%	13%	3%	38%	55%	3%	100%	4%	49%	31%	24%	64%
Pt Drugs	11	73%	73%	55%	100 %	0%	0%	9%	0%	0%	0%	9%	9%	27%	9%	36%	9%	45%	55%	18%	82%	100%	36%	45%	9%	3%
AI	131	67%	89%	56%	87%	21%	6%	12%	5%	7%	4%	11%	9%	19%	7%	11%	2%	56%	60%	4%	86%	3%	100%	47%	26%	36%
ART	93	69%	258%	58%	83%	19%	5%	17%	8%	10%	6%	14%	11%	17%	8%	14%	4%	87%	85%	4%	76%	5%	66%	100%	25%	26%
Other	90	66%	76%	58%	84%	18%	7%	17%	12%	7%	7%	10%	4%	18%	8%	11%	2%	32%	43%	2%	62%	1%	38%	26%	100%	25%

Table 3.5 Logistic regression of CAM used during any attempt

	Unadjusted OR [95% CI]	**Adjusted OR [95% CI]**
Recruitment Site		
Population	Reference	Reference
Clinic	1.22 [0.92-1.62]	0.7 [0.48-1.02]
Age at 1st attempt		
<25	Reference	Reference
>=25	0.95 [0.70-1.28]	0.91 [0.63-1.32]
BMI Category		
Underweight/Normal	Reference	Reference
Overweight/ Obese	0.82 [0.61-1.11]	0.86 [0.6-1.21]
Annual Income		
Less than $50,000	Reference	Reference
50,000-$99,999	0.92 [0.67-1.27]	0.71 [0.48-1.06]
Over $100,000	1.05 [0.66-1.68]	0.8 [0.44-1.45]
Education Level		
Less than college grad	Reference	Reference
College grad or more	0.95 [0.70-1.28]	1.03 [0.71-1.49]
Race/Ethnicity		
White, Non-Hispanic	Reference	Reference
Hispanic, Other Non-White	1.18 [0.66-2.11]	1.25[0.6-2.6]
Religion		
Non-LDS	Reference	**Reference**
Latter-Day Saint	0.86 [0.62-1.20]	**0.64 [0.42-0.98]**
Pregnancy		
No pregnancy	Reference	Reference
Pregnancy	0.81 [0.60-1.09]	0.71 [0.49-1.02]
Longest Attempt Duration		
<24 months	**Reference**	Reference
24 months or longer	**2.01 [1.39-2.92]**	1.41 [0.9-2.22]
Other Treatments/Interventions ever used		
Fertility Focused Intercourse*	**8.15 [2.5-26.45]**	**4.47 [1.31-15.2]**
Drugs*	**2.59 [1.81-3.71]**	1.5 [0.95-2.38]
AI*	**2.60 [1.93-2.49]**	**1.57 [1.05-2.36]**
ART*	**2.48 [1.84-3.32]**	**2.52 [1.72-3.69]**
*Reference is never using these interventions		

Table 3.6 Logistic regression of medical interventions used during any attempt.

	Unadjusted OR [95% CI]	**Model 1. Adjusted OR [95% CI]**	**Model 2. Adjusted OR [95% CI]**
Recruitment Site			
Population	Reference	**Reference**	**Reference**
Clinic	7.69 [4.90-12.08]	**9.36 [5.23-16.77]**	**9.12 [5.09-16.35]**
Age at 1st attempt			
<25	Reference	Reference	Reference
≥25	1.17 [0.82-1.66]	1.02 [0.65-1.6]	1.03 [0.65-1.61]
BMI Category			
Underweight/Normal	Reference	Reference	Reference
Overweight/ Obese	1.18 [0.82-1.69]	1.45 [0.95-2.2]	1.38 [0.9-2.11]
Annual Income			
Less than $50,000	**Reference**	Reference	Reference
50,000-$99,999	**1.66 [1.15-2.42]**	1.34 [0.85-2.1]	1.27 [0.80-2.00]
Over $100,000	**2.15 [1.17-3.97]**	1.75 [0.8-3.81]	1.82 [0.82-4.07]
Education Level			
Less than college grad	Reference	Reference	Reference
College grad or more	1.11 [0.78-1.58]	1.15 [0.73-1.79]	1.09 [0.69-1.71]
Race/Ethnicity			
White, Non-Hispanic	Reference	Reference	Reference
Hispanic, Other Non-White	0.76 [0.39-1.49]	0.6 [0.25-1.43]	0.66 [0.27-1.58]
Religion			
Non-LDS	Reference	**Reference**	**Reference**
Latter-Day Saint	1.43 [0.98-2.10]	**2.05 [1.25-3.34]**	**1.93 [1.17-3.17]**
Pregnancy			
No pregnancy	**Reference**		**Reference**
Pregnancy	**1.43 [1.01-2.04]**		**1.69 [1.08-2.66]**
Longest Attempt Duration			
<24 months	**Reference**	**Reference**	**Reference**
≥24 months	2.79 [1.94-4.02]	**2.28 [1.46-3.55]**	**2.66 [1.66-4.26]**

Table 3.7 Association between different types of intervention, adjusted for demographic and reproductive factors (logistic regression models)

	Adjusted OR [95% CI] Fertility focused intercourse	**Adjusted OR [95% CI] Weight and diet**	**Adjusted OR [95% CI] Complementary alternative medicine**	**Adjusted OR [95% CI] Medical interventions**
Longest Attempt Duration				
<24 months	Reference	Reference	Reference	Reference
24 months or longer	1.32[0.62-2.82]	0.88 [0.56-1.36]	**1.90 [1.22-2.97]**	**1.93 [1.21-3.07]**
Other Interventions ever used				
Fertility focused intercourse	NA	**4.76 [1.52-14.88]**	**4.06 [1.18-13.99]**	**5.09 [2.41-10.75]**
Weight and diet	**4.39 [1.40-13.81]**	NA	**4.54 [3.11-6.63]**	1.21 [0.72-2.03]
Complementary-alternative medicine	**3.74 [1.07-12.06]**	**4.57 [3.13-6.68]**	NA	**1.89 [1.11-3.20]**
Medical interventions	**5.18 [2.38-11.27]**	1.26 [0.76-2.12]	**1.94 [1.15-3.28]**	**NA**

*Reference is never using this intervention

*Each column is a separate logistic regression model, and in addition to the variables shown is adjusted for recruitment site, age, body-mass index, income, education, race/ethnicity, religion

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CHAPTER 4

FERTILITY TREATMENTS AND THE RISK OF PRETERM BIRTH AMONG WOMEN WITH SUBFERTILITY

4.1 Abstract

The objective of this aim is to determine the effect of fertility treatment (in vitro fertilization (IVF), intrauterine insemination (IUI), usually with ovulation drugs (IUI), or ovulation drugs alone) on preterm birth, compared to no treatment in subfertile women. To achieve this aim we used parallel retrospective population and clinic cohorts linked to birth certificate data. Women with a history of primary subfertility were linked to first birth or fetal death record within the state of Utah (N = 491). Self-reported fertility treatments, diagnoses, and duration of subfertility were obtained from online and telephone questionnaires. Participants were linked to birth certificates and fetal death records for data on perinatal outcomes.

A total 487 birth certificates and three fetal death records were linked as first births for study participants who completed questionnaires. Among linked births, 19% were PTB. After adjustment for maternal age, paternal age, maternal education, annual income, religious affiliation, female or male fertility diagnosis, and duration of subfertility, the odds ratios and 95% confidence intervals (CI) for PTB were 2.2 (95% CI 1.0-4.8) for births conceived using ovulation drugs, 3.2 (95% CI 1.4-7.2) for neonates

conceived using IUI, and 4.2 (95% CI 2.1-8.8) for neonates conceived by IVF, compared to women with subfertility who used no treatment during the month of conception. A reported diagnosis of female factor infertility increased the adjusted odds of having a PTB 3.0 (95% CI 1.5-6.0). Duration of pregnancy attempt was not independently associated with PTB. In restricting analyses to singleton gestation, odds ratios remained elevated but were not significant for any type of treatment.

IVF, IUI, and ovulation drugs were all associated with a higher incidence of preterm birth and low birth weight, predominantly related to multiple gestation births. The findings support changes to treatment protocols to maximize singleton gestation and consideration of risks for pregnancies conceived using any medical fertility treatment, not just ART.

4.2 Introduction

Approximately one in every seven couples experiences difficulty conceiving or maintaining a pregnancy; this prolonged duration of nonconception is referred to as subfertility.[1-4] Subfertility is commonly identified as a clinical "infertility" when a couple desiring conception has had regular unprotected intercourse for 12 months or longer without achieving pregnancy.[1] There are varying degrees of subfertility and a variety of potential underlying causes: abnormalities in oocyte production, abnormalities in sperm production, abnormalities in reproductive tract transport of the sperm, oocyte, and/or embryo, abnormalities in the implantation process, or other conditions that affect one or multiple components of the reproductive process.[5] Diagnostic tests and tracking menstrual cycle patterns can help to determine the underlying etiology of the

unsuccessful pregnancy attempts.[6] However, frequently providers are unable to identify the precise cause of a couple's subfertility and in 15-30% of cases assign more ambiguous diagnosis of unexplained infertility.[7]

About half of subfertile couples seek medical treatment.[8] Common medical approaches to overcoming subfertility include the use of in vitro fertilization (IVF), intrauterine insemination (IUI), and ovulation stimulation (OS). In the past 3 decades, the focus of fertility research and treatment has increasingly shifted from less invasive medical treatments (including OS and IUI) to more invasive, specifically IVF. IVF was originally developed to overcome absolute subfertility due to blockage or absence of the fallopian tubes and later expanded to treat severe male subfertility with the addition of intracytoplasmic sperm injection (ICSI) (i.e., specific indications for IVF), but is now frequently used for couples with diminished fertility due to any cause as well as those with infertility of unknown cause.[9, 10] While some advocate that IVF should become a primary management strategy for couples without specific indications because of its high probability of success per cycle success, there are substantial concerns about expanding use of IVF, including high cost and impact on neonatal outcomes.[9, 10] Epidemiologic studies have demonstrated higher incidence of preterm birth (PTB), low birthweight (LBW), and birth defects among children conceived through IVF, when compared to children conceived naturally, even when the analyses are limited to singleton pregnancies.[11-13]

In the United States, the Society of Assisted Reproductive Technology (SART) and the Center for Disease Control conduct fertility clinic level surveillance with the goal of tracking IVF procedures and outcomes.[14, 15] The proportion of live births conceived

through IVF average 1.4% but vary by region (range: 0.2% in Puerto Rico to 4.3% in Massachusetts)[16]; however, across the nation IVF births contribute to a considerable proportion of the PTB and LBW infants born each year. No formal surveillance exists for the less invasive treatments, but exposure to these fertility treatments (OS and IUI) may also be associated with adverse perinatal outcomes.[17-19] It is estimated that OS accounts for up to 6% of the births in the United States and about 1% of births results from IUI.[17, 20] However, monitoring birth outcomes and assessing risks associated with each of these medical exposures are critical public health concerns. Additional questions remain as to whether these adverse outcomes are related to the treatments or to the underlying causes or severity of the subfertility.[11, 21] Few studies exist that assess the independent risks of subfertility.[12]

This research aims to provide insight into the relationship between fertility treatments (OS, IUI, and IVF) and preterm birth among women with primary subfertility compared to subfertile women who conceived without fertility treatment. We used data from parallel clinic and population-based cohorts, and examined the contribution of pregnancy attempt duration and fertility-related diagnoses, as well as the role of multiple gestations.

4.3 Methods

4.3.1 Study Population and Data

The Fertility Experiences Study (FES) is a retrospective cohort study conducted at the University of Utah between April 2010 and September 2012. Two parallel cohorts were recruited. For the clinic-based cohort, participants were recruited from female

patients seen for a new consultation for subfertility and/or treatment at one of two specialty fertility clinics in Utah between 2000 and 2009. For the population-based cohort, two period based cohorts were recruited using the Utah Population Database (UPDB) to identify and recruit potentially eligible women of reproductive age range who were married as of 2002 or 2006 but had not yet had a live birth as of the end of 2004 or 2008 (index dates).[22] For both clinic and population-based cohorts, the final eligibility criteria were as follows: between 20-35 years of age at the index date, no pregnancies prior to index date, at least one year of regular intercourse without contraception with a male partner at the index date, and a Utah resident during three years following the index date. All participants in the study completed the Fertility Experiences Questionnaires (FEQ), which included a self-administered online questionnaire followed by a structured telephone interview with trained study staff. In preparatory research in comparison to medical records, the FEQ was over 90% sensitive for pregnancy attempt duration, pregnancy outcomes, and use of IVF and IUI and 70% sensitive for the use of ovulation drugs (Thomas et al

, in review). Data from 2000 to 2010 Utah birth and fetal death certificates were linked with data from women who completed both the online questionnaire and the structured telephone interview. The University of Utah Institutional Review Board approved this study.

4.3.2 Classification of Exposure Status

The key exposure measure is the type of fertility treatment received during the month of conception that resulted in the first live birth or fetal death. Treatment groups

are defined based on the most invasive medical treatment used during the cycle of conception. For the purposes of this study, the most invasive treatment is IVF. IVF includes all procedures that involve manipulating both sperm and eggs outside the body. The next most invasive treatment was considered to be IUI. Women were categorized as using IUI during the cycle of conception, regardless of if they were also using OS. If women only reported medication to stimulate or enhance ovulation during the conception cycle, then they were classified as using OS. Women who did not receive any medication or procedure during the cycle of conception were classified as having no treatment, even if they receive medical treatment during previous cycles or reported alternative nonmedical treatment (such as acupuncture or herbs). This group of untreated subfertile women was used as the control for the analysis.

We assessed the duration of pregnancy attempt duration, which provides an indicator of severity of subfertility. During the structured telephone interview, trained study staff asked each woman about specific dates when she was at risk for pregnancy. Pregnancy attempt duration was calculated as the interval between the date that the attempt began and the estimated date of conception. The estimated date of conception was calculated using birth certificate data for clinical gestational age at birth and date of birth.

Fertility-related diagnoses were obtained through the self-administered online questionnaire. The question asked "have you or your partner ever been told or suspect that you have any of the following diagnosis?" Answers were yes, no, and unsure. Women who answered no or they were unsure were considered to have a negative answer. For this analysis, diagnoses were grouped into the Society for Assisted

Reproductive Technology Clinical Outcomes Reporting System (SARTCORS) categories. SARTCORS categories are tubal factor, endometriosis, ovulation dysfunction, uterine factor, male factor, or unexplained. If women have more than one female factor diagnosed, then they are categorized as multiple female factors. If a couple has a female contributor and a male factor issue, then they are categorized as combined male and female factor. For this analysis, any female factor infertility was collapsed into a dichotomous variable, and any male factor was considered a separate dichotomous variable.

4.3.3 Outcome Definition

The primary outcome measure was preterm birth. PTB is defined as any pregnancy that ended in a live birth or fetal death at less than 37 completed weeks of gestation as reported on the state birth certificate.[23] Birth certificate gestational age is typically calculated by the hospital using last menstrual period, confirmed by first trimester ultrasound. The occurrence of multiple gestations was also obtained from the birth certificate or fetal death certificate. In the state of Utah fetal death certificates are issued for in-utero demise after 20 weeks gestation.

4.3.4 Covariates

Covariates for the analysis were based on known risk factors for fertility treatments and for preterm birth. Variables considered in the analysis include age of mother at delivery, age of male partner, maternal education, prepregnancy BMI, annual income, and religious affiliation. Religious affiliation with the Church of Jesus Christ of

Latter-day Saints (LDS) was identified because of its strong association with avoiding behavioral risk factors such as tobacco use, alcohol use, and drug use.[24] Parental age and maternal BMI were obtained from the birth certificate. Parental age was categorized as less than 30 years or 30 years old or older at the time of delivery. BMI was calculated using prepregnancy weight and height and dichotomized as underweight/normal BMI ($<25 kg/m^2$) and overweight/obese BMI ($\geq 25 kg/m^2$). Education, income, and LDS religious affiliation were obtained from the FEQ. Education was dichotomized as less than college graduation and college graduation or more. Income was grouped as annual household income of less than $50,000, $50,000-$99,000, and $100,000.

4.3.5 Statistical Analysis

The frequency of PTB was compared across participant characteristics and exposure variables. Crude and adjusted odds ratios and 95% confidence intervals for each individual outcome were estimated using simple and multivariable logistic regression. Parental age, prepreganancy BMI, education, income, LDS religious affiliation, and treatment received during the cycle of conception were included in the base model. Subsequent models assessed exposures including extended duration of pregnancy attempt (less than 24 months versus 24 months or more), self-reported diagnosis categories (female and male factor categories), and multiple gestation dichotomized. We repeated the analyses limited to singletons.

4.3.6 Sensitivity Analysis

In sensitivity analysis, age, BMI, and duration of attempt were also analyzed as continuous variables. We performed an analysis, removing participants who reported fertility related diagnosis related to tubal factors, as these women would not have been able to conceive without treatment by IVF. Additional sensitivity analysis was conducted for women who were subfertile using the screening question but may have had intervening breaks in their pregnancy attempt (due to birth control for personal or medical use, miscarriage, or other reasons) so that their discrete attempt leading up to their first birth was found to be less than 12 months.

4.4 Results

Study participants reported a total of 492 first births in the FEQ telephone interview. Of these, 491 were linked to state vital records—488 came from birth certificates and three came from fetal death records (Figure 4.1). Of the live births, 18.8% were preterm. Table 4.1 displays the distribution of maternal characteristics and demographics by PTB outcomes.

In this cohort of women achieving a live birth, 41% reported having unexplained infertility, 40% reported male factor infertility, 54% reported a diagnosis of ovulation dysfunction, 27% endometriosis, 16% a tubal factor, 13% uterine faction infertility, 29% multiple female factors, 12% blocked or damaged fallopian tubes, and 27% male factor subfertility (not mutually exclusive). Types of treatments used during the cycle of conception did not vary significantly for women who reported tubal factor, endometriosis, or unexplained infertility. However, women who reported ovulatory

dysfunction more often reported OS medication during the conception cycle compared to other treatments, women with uterine factor most frequently reported IVF, and women with unexplained infertility most commonly reported not using any treatment during the cycle of conception (Table 4.2). Women who suspected or were told by a provider they had tubal factor infertility had a higher incidence of PTB than women without tubal factor (27% versus 17%; p-value < 0.05). Women with multiple female factor diagnosis were also found to have more PTB than women without multiple female factors (25% versus 17%; p-value < 0.05). Women with endometriosis had a nearly significant higher incidence of PTB compared to women without endometriosis (24% versus 17%; p-value = 0.053) (Table 4.3).

About 44% of the subfertile women conceived while not using any medical treatment during the cycle of conception, whereas 16% reported use of ovulation-enhancing drugs, 13% used IUI, and 28% conceived using IVF. Many women reported use of more invasive treatments outside the cycle of conception. For example, of women who conceived using no treatment, 15% reported unsuccessfully using OS previously, 16% had tried IUI, and 16% had tried IVF (Table 4.4).

In the unadjusted logistic regression analysis, the risk of preterm birth was 2 times higher (95% CI 1.3-3.4) for women recruited from the specialty subfertility clinics than women from the general population. All types of treatment used during the cycle of conception were also associated with increased odds of PTB in the unadjusted model when compared to women that conceived spontaneously. Multiple gestation birth was 22 times as likely to occur at less than 37 weeks gestation (95% CI 12.3-39.8) in the unadjusted model.

After adjustment for maternal age, paternal age, maternal education, annual income, religious affiliation, female or male fertility diagnosis, and duration of subfertility, the odds of having a PTB were 2.2 times higher (95% CI 1.0-4.8) for women who conceived using ovulation drugs, 3.2 times higher (95% CI 1.4-7.2) for women who conceived using IUI and 4.2 time higher (95% CI 2.1-8.8) for women who conceived by IVF, compared to women with subfertility who used no treatment during the month of conception. Duration of pregnancy attempt was not independently associated with PTB. A reported diagnosis of female factor infertility increased the adjusted odds of having a PTB was 3.0 times higher (95% CI 1.5-6.0) compared to women who did not report any female factor infertility. Although slightly attenuated when excluding women with tubal factor, the odds of PTB were still significant (aOR 2.75; 95% CI 1.42-5.31) for women with any female factor infertility. Only 6.6% of the births conceived without any treatment during the month of conception were twins, for OS this increased to 19% twins and 6% triplets, IUI births were 10.9% twins and 5% triplets, and IVF births were 30% twins and 2% triplets. Multiple gestations had the highest association with adverse neonatal outcomes (aOR 28.0; 95% CI 15.6-68.6) when controlling for all other variables. In restricting analyses to singleton gestation, odds ratios remained elevated but were no longer significant for any type of treatment (Table 4.5). However, female factor infertility was found to be independently associated with PTB when controlling for treatment, multiple gestations, and other potential confounders.

4.5 Discussion

When compared to subfertile women who did not use any fertility treatments during the cycle of conception, women who used any kind of fertility treatment were more significantly more likely to deliver preterm. As the invasiveness of treatment increased, so did both the incidence of multiple gestations and the incidence of PTB. Women who used OS to conceive were more than 2.5 times as likely to deliver preterm compared to women who used no treatment. Women who conceive using IUI and IVF are about 3.5 times as likely to experience a PTB as the subfertile women who do not use any treatment. Multiple gestations had the highest association with PTB. An independent association between female factor infertility etiology and PTB was also uncovered even when controlling for multiple gestations. This study may have been underpowered to examine the impact of specific diagnosis on PTB risk (i.e, endometriosis and tubal infertility) and of the impact of fertility treatment on PTB in singleton births. Other recent population-based research has indicated an association of IVF with PTB among singletons.[12]

These findings are consistent with previous literature that used birth registries to look at non-IVF births among women who were subfertile.[21] Our findings are consistent with findings from Danish national registries that saw a marked increased in PTB in births conceived through IUI.[25] Research examined "low-technology" treatment and determined an increased risk of PTB as well as a history of research that has seen an increase risk of PTB among births conceived through IVF.[11, 18, 25, 26] Few studies have compared birth outcomes of subfertile women conceiving with fertility treatments with subfertile women who conceive spontaneously.[12] The use of an untreated subfertile

population as the referent category for a variety of treatment exposures is a strength of this study and may present a treatment effect magnitude that at least partially controls for misclassification of fertility related diagnosis and undiagnosed subfertility pathology.

Limitations of this study include the retrospective assessment of exposure that may result in both differential and nondifferential problems with recall. We sought to minimize problems with recall for treatment by the multimode, two stage FEQ. Additionally, there are some limitations in the accuracy of gestational age from birth certificates, which should be acknowledged, but these clinically relevant estimates are typically confirmed with early ultrasound. We did not distinguish between spontaneous labor and iatrogenic labor for women delivering at less than 37 weeks gestation: in future studies we recommend that this be taken into account.

Generalizability of findings may also be limited by the geographic location with a relatively homogenous racial and ethnic population. However, this homogenous population also allows for a more direct effect of the exposures to be evaluated as many of the unmeasured environmental, social, and genetic factors may be controlled for through sampling.

PTB is a significant public health issue worldwide. In the United States more than 11% of live born infants are born at gestational ages <37 weeks. PTB contributes largely to infant and child morbidity and mortality.[27, 28] More than 26.2 billion dollars are spent in the United States each year on costs associated with PTB.[23] The findings from this analysis suggest that all medical fertility treatments, as practiced in this State, contribute directly to the incidence of PTB, principally by increasing multiple births. Efforts should be made to reduce the incidence of multiple gestations from all fertility treatments, not

just IVF.[29, 30] However, based on these and other data, we cannot exclude the possibility that even if all multiple gestations are eliminated, there may remain some risk for preterm birth among singletons.[12] Thus, we support the need for more rigorous population surveillance on the use of all fertility treatments, not just IVF.[31]

We suggest that women who are experiencing difficulty conceiving should consider first the opportunity for conception with less invasive treatments or no treatment. Although the time to conception may be longer, the potential for improved optimal birth outcomes should be weighed strongly against the desire to conceive faster. Additional research needs to be conducted to assess time to live birth in subfertile populations using a variety of fertility treatments.[32] The risk of PTB after conception using OS or IUI is increased on an even greater magnitude to smoking, yet clinicians and patients may pay less attention to the risk of treatment.[33, 34]

In conclusion, our findings support efforts to encourage women to give an adequate trial of the least invasive fertility treatment that may work for them, to modify the practice of all fertility treatments to minimize incidence of multiple gestation and to increase vigilance during prenatal care for pregnancies of all women with subfertility, regardless of treatment received. Future research should consider interventions that may prevent preterm birth among these higher risk populations of subfertile women conceiving using any fertility treatments.

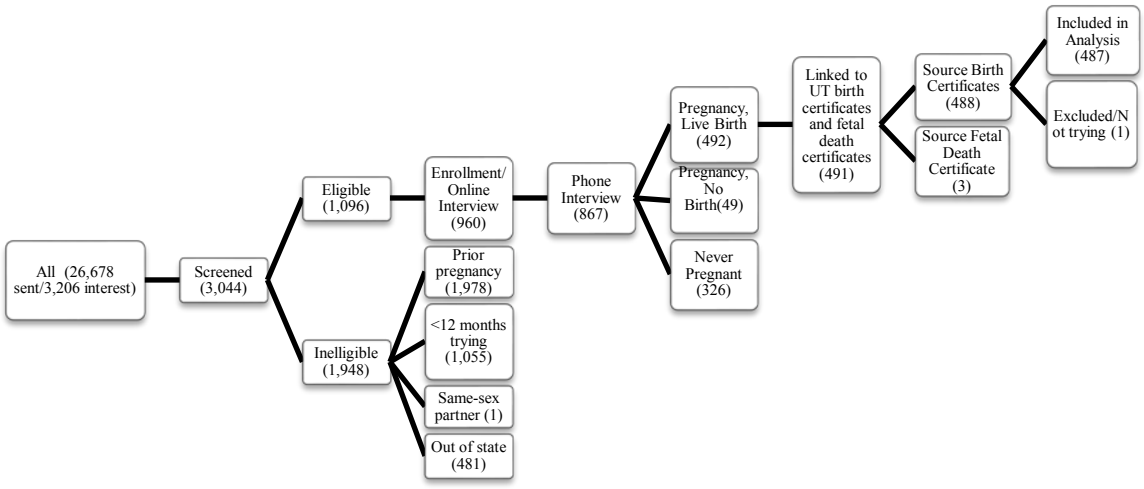

Figure 4.1 Flowchart of study participation, pregnancy outcome, and data linkage

Table 4.1 Characteristics of women by preterm birth (<37 weeks gestational age)

	Term (>37 wks)		Preterm (<37 wks)		Total		P-Value
	N	Row%	N	Row%	N	Col%	
Maternal Age at delivery							
≤30	290	81.7%	65	18.3%	355	72.4%	0.669
31+	108	80.0%	27	20.0%	135	27.6%	
Paternal age at delivery							
≤30	239	83.0%	49	17.0%	288	58.9%	0.223
31+	158	78.6%	43	21.4%	201	41.1%	
BMI Category (pre-pregnancy)							
Underweight/Normal	184	76.0%	58	24.0%	242	55.1%	0.148
Overweight/Obese	161	81.7%	36	18.3%	197	4.9%	
Income (at Interview)							
Less than $50,000	110	81.5%	25	18.5%	135	28.7%	0.938
50,000-$99,999	213	80.1%	53	19.9%	266	56.6%	
Over $100,000	56	81.2%	13	18.8%	69	14.7%	
Education Level (at Interview)							
Less than college grad	127	77.4%	37	22.6%	164	33.6%	0.136
College grad or more	269	83.0%	55	17.0%	324	66.4%	
Race/Ethnicity							
White, Non-Hispanic	381	80.9%	90	19.1%	471	96.1%	0.348
Hispanic, Other Non-White	17	89.5%	2	10.5%	19	3.9%	
Religion							
Non-LDS	84	78.5%	23	21.5%	107	21.8%	0.415
Latter-Day Saint	314	82.0%	69	18.0%	383	78.2%	
Insurance Coverage for Tx or DX							
None or unsure	40	88.9%	5	11.1%	45	9.2%	0.330
Some insurance coverage	101	82.1%	22	17.9%	123	25.1%	
Not asked	257	79.8%	65	20.2%	322	65.7%	
Attempt duration to conception							
<12mo	69	81.2%	16	18.8%	85	17.4%	0.771
12-<24	100	81.3%	23	18.7%	123	25.2%	
24-<36	73	85.9%	12	14.1%	85	17.4%	
36-<48	58	79.5%	15	20.5%	73	14.9%	
48+	97	78.9%	26	21.1%	123	25.2%	
Recruitment Cohort							
Clinic	203	76.3%	63	23.7%	266	54.3%	**0.002**
Population	195	87.1%	29	12.9%	224	45.7%	
Baby sex							
F	188	79.0%	50	21.0%	238	48.6%	0.219
M	210	83.3%	42	16.7%	252	51.4%	
Multiplicity							
Singleton	374	90.8%	38	9.2%	412	84.1%	**0.000**
Twins	24	33.8%	47	66.2%	71	14.5%	
Triplets	0	0.0%	7	100.0%	7	1.4%	
Successful Tx							
None	190	89.2%	23	10.8%	214	43.5%	**0.001**
Drugs	61	79.2%	16	20.8%	77	15.7%	
IUI	48	75.0%	16	25.0%	64	13.1%	
IVF	99	72.8%	37	27.2%	136	27.8%	
Total	398	81.2%	92	18.8%	490	100.0%	

Table 4.2 Treatment during the conception cycle by infertility etiology (N = 490)

	None		Drugs		IUI		IVF		Total		P-value
	N	Row%	N	Row%	N	Row%	N	Row%	N	Col%	
Tubal Factor	29	37.2%	14	17.9%	9	11.5%	26	33.3%	78	15.9%	0.550
Endometriosis	49	37.4%	18	13.7%	19	14.5%	45	34.4%	131	26.7%	0.169
Ovulation Dysfunction	99	37.5%	63	23.9%	41	15.5%	61	23.1%	264	53.9%	**0.000**
Uterine Factor	20	30.8%	7	10.8%	12	18.5%	26	40.0%	65	13.3%	**0.022**
Male Factor	60	30.8%	21	10.8%	27	13.8%	87	44.6%	195	39.8%	**0.000**
Unexplained infertility	136	47.4%	43	15.0%	32	11.1%	76	26.5%	287	59.5%	0.176
Multiple Female Factors	45	32.6%	26	18.8%	25	18.1%	42	30.4%	138	28.2%	**0.014**
Multiple Female and Male	43	33.1%	19	14.6%	16	12.3%	52	40.0%	130	26.5%	**0.002**
Total	213	43.5%	77	15.7%	64	13.1%	136	27.8%	490	100.0%	

Table 4.3 Birth outcomes by reported infertility etiology (N = 490)

	Term		Preterm		Total		P-Value
	N	Row%	N	Row%	N	Col%	
Tubal Factor							
No	341	82.8%	71	17.2%	412	84.1%	**0.044**
Yes	57	73.1%	21	26.9%	78	15.9%	
Endometriosis							
No	299	83.3%	60	16.7%	359	73.3%	0.053
Yes	99	75.6%	32	24.4%	131	26.7%	
Ovulation Dysfunction							
No	190	84.1%	36	15.9%	226	46.1%	0.135
Yes	208	78.8%	56	21.2%	264	53.9%	
Uterine Factor							
No	347	81.6%	78	18.4%	425	86.7%	0.540
Yes	51	78.5%	14	21.5%	65	13.3%	
Male Factor							
No	243	82.4%	52	17.6%	295	60.2%	0.423
Yes	155	79.5%	40	20.5%	195	39.8%	
Unexplained infertility							
Yes	156	80.0%	39	20.0%	195	40.5%	0.604
No	235	81.9%	52	18.1%	287	59.5%	
Multiple Female Factors							
No	294	83.5%	58	16.5%	352	71.8%	**0.037**
Yes	104	75.4%	34	24.6%	138	28.2%	
Multiple Female and Male Factors							
No	299	83.1%	61	16.9%	360	73.5%	0.084
Yes	99	76.2%	31	23.8%	130	26.5%	
Total	398	81.2%	92	18.8%	490	100.0%	

*chi2 comparing to women who were not told or suspect diagnosis

- Diagnostics Categories--**SART CORS classification**
  - **Tubal Factor**—pelvic adhesion or scarring, blocked or damaged fallopian tubes
  - **Endometriosis**
  - **Ovulation dysfunction-**low progesterone, low estrogen, not ovulating, abnormal ovulation , lutenized unruptured follicule (LUF), Luteal Phase Defect (LUD), PCOS
  - **Uterine Factor**—hostile or limited cervical mucus, fibroids in the uterus, polyps in the uterus,
  - **Male Factor**
  - **Unknown- Unexplained Subfertility**
  - **Multiple Female Factor-** More than one of the following diagnosis Tubal, Endometriosis, Ovulation dysfunction, or Uterine
  - **Female and Male Factor-** Male factor plus at least one female factor

Table 4.4 Fertility treatments used during the month of conception and most invasive fertility treatment used previously

	Most invasive treatment during conception attempt but not during conception cycle					
Intervention used during conception cycle		None	Drugs	IUI	IVF	**Total**
	None	51.6%	14.7%	16.1%	15.7%	**213**
	Drugs	0.0%	83.6%	13.7%	8.2%	**77**
	IUI	0.0%	0.0%	93.8%	6.3%	**64**
	IVF	0.0%	0.0%	0.0%	100.0%	**136**
	Total	**113**	**92**	**105**	**180**	**490**

Table 4.5 Multivariable logistic regression models for risk of preterm birth

	Unadjusted OR [95% CI]	Model 1: aOR [95% CI]	Model 2: aOR [95% CI]	Model 3: aOR [95% CI]	Model 4: aOR [95% CI]*
Maternal age at Delivery					
≤30	Reference	Reference	Reference	Reference	Reference
31+	1.11 [0.68-1.83]	1.02 [0.51-2.04]	1.03 [0.5-2.09]	0.91 [0.38-2.19]	0.41 [0.13-1.28]
Paternal age at Delivery					
≤30	Reference	Reference	Reference	Reference	Reference
31+	1.33 [0.84-2.09]	1.39 [0.74-2.62]	1.54 [0.8-2.97]	1.42 [0.64-3.13]	2.55 [0.98-6.65]
BMI Category (at delivery)					
Underweight/Normal	Reference	Reference	Reference	Reference	Reference
Overweight/ Obese	0.94 [0.57-1.54]	0.93 [0.55-1.59]	0.9 [0.52-1.55]	1.19 [0.61-2.33]	1.72 [0.75-3.95]
Income					
Less than $50,000	Reference	Reference	Reference	Reference	Reference
50,000-$99,999	1.09 [0.65-1.86]	1.09 [0.58-2.04]	1.13 [0.6-2.14]	0.81 [0.38-1.72]	1.28 [0.5-3.24]
Over $100,000	1.02 [0.49-2.15]	0.73 [0.29-1.86]	0.71 [0.28-1.84]	0.85 [0.27-2.73]	1.16 [0.28-4.87]
Education Level					
Less than college grad	Reference	Reference	Reference	Reference	Reference
College grad or more	0.70 [0.44-1.12]	0.67 [0.39-1.16]	0.7 [0.4-1.23]	0.84 [0.42-1.67]	0.45 [0.2-1.05]
Religion					
Non-LDS	Reference	Reference	Reference	Reference	Reference
Latter-Day Saint	0.80 [0.47-1.36]	0.85 [0.45-1.62]	0.87 [0.45-1.67]	0.73 [0.32-1.66]	0.85 [0.31-2.28]
Most Invasive Tx used during cycle of conception					
None	Reference	Reference	Reference	Reference	Reference
Drugs	**2.17 [1.08-4.36]**	**2.68 [1.25-5.76]**	**2.17 [0.99-4.75]**	1.34 [0.52-3.45]	1.08 [0.34-3.4]
IUI	**2.75 [1.35-5.61]**	**3.5 [1.57-7.83]**	**3.17 [1.4-7.19]**	2.16 [0.82-5.69]	1.98 [0.65-6.04]
IVF	**3.09 [1.74-5.48]**	**3.6 [1.86-7]**	**4.24 [2.05-8.77]**	1.46 [0.59-3.58]	1.45 [0.48-4.37]
Attempt duration ending in conception					
<24	Reference		Reference	Reference	Reference
≥24	1.01 {0.64-1.59]		0.59 [0.33-1.06]	0.66 [0.33-1.34]	0.69 [0.3-1.6]
Etiology					
No Female Factor			Reference	Reference	Reference
Any Female Factor			**2.99 [1.5-5.97]**	**3.00 [1.32-6.79]**	**4.9 [1.4-17.1]**
No Male Factor			Reference	Reference	Reference
Any Male Factor			1.01 [0.58-1.76]	0.99 [0.51-1.95]	1.34 [0.57-3.13]
Multiple Gestation					
Singleton	Reference			Reference	
Multiple	22.14 [12.3-39.79]			**27.91 [13.25-58.79]**	
Model 1:maternal age, paternal age, prepregnancy BMI, Income, education, Religion, Infertility treatment used during month of conception					
Model 2: maternal age, paternal age, prepregnancy BMI, Income, education, Religion, Infertility treatment used during month of conception					
Model 3: maternal age, paternal age, prepregnancy BMI, Income, education, Religion, Infertility treatment used during month of conception, duration of infertility, female factor (ovulatory dysfunction, endometriosis, tubal factor, uterine factor), male factor fertility etiology, multiples					
Model 4: maternal age, paternal age, prepregnancy BMI, Income, education, Religion, Infertility treatment used during month of conception, duration of infertility, female factor (ovulatory dysfunction, endometriosis, tubal factor, uterine factor), male factor fertility etiology--limited to singletons (n=353)					

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CHAPTER 5

CONCLUSION AND FUTURE DIRECTIONS

5.1 Summary of Key Findings

Aim 1 compared longest pregnancy attempt recall based on three different questioning approaches among women with a history of subfertility. The first approach uses a standard single question (single question approach); the second approach is a series of questions assessing discrete pregnancy attempts using specific dates for start and stop time at risk (date approach), and the third approach asks the woman for a date when she began "actively" trying to become pregnant (active date approach). We found that misestimation of longest single attempt duration occurred frequently when information was solicited using the common single question approach. Only a third (34%) of women accurately reported their longest attempt duration based on this single question when compared to information obtained using the date-based approach (+/- 3 months), while 37% of women overestimated and 29% of women underestimated their TARP using the single question approach. Women who *overestimated* their longest attempt with the single question approach were older when their first attempt started, had higher BMIs, and had longer time intervals between their first attempt and the time of the interview than women who accurately estimated their TARP. Women who *underestimated* their TARP were older when their first attempt started, had lower educational attainment, and

had a longer time interval between the start of their first attempt and the date of the interview than those who accurately estimated. The risk of misestimation was significantly lower for women who had experienced a pregnancy (with or without live birth).

Aim 2 describes use of behavioral, nonmedical, and medical interventions reported by women who experienced primary infertility. Women commonly use a mix of medical and nonmedical interventions while trying to conceive. Nearly all participants (94%) engaged in fertility-focused intercourse methods during at least one pregnancy attempt. A third of women (35%) either lost weight or changed their diet with the intention of enhancing their fertility. A third of women (n = 287) also reported using CAM in at least one attempt but only 4% (n = 31) reported CAM as their most invasive treatment. There was a high rate of medical treatment used in this population, with 81% (n = 703) reporting some type of medical treatment, including OS, IUI, and/or ART. Rates of partner-focused interventions were low in both cohorts. The most common intervention used by male partners was weight loss (6%). Women reported that male partners also used fertility diets (5%), vitamins (6%), herbs (5%), acupuncture (2%), medications such as Clomid (3%), and hormonal treatments (3%). Overall, only 15% (n = 133) of women in this cohort never used any intervention to enhance their fertility. Compared to women recruited from specialty infertility clinics, women from the general population were less likely to use any type of medical treatment, but equally likely to use nonmedical interventions. During the pregnancy attempt history, women frequently reported using more than one method to enhance their fertility. The average number of interventions used was 3.4, but ranged from 0 to 8 (potential maximum is 9). Women

recruited from the specialty clinics used different types of treatments than women recruited from the general population; however, there was no difference in the proportion of women achieving at least one pregnancy in the two groups (64% versus 63%; p = 0.76). There were significantly more clinic-recruited women who had at least one pregnancy ending in a multiple gestation birth compared to women recruited from the population (23% versus 11%; p-value < 0.01).

Aim 3 examined the effect of fertility treatment OS, IUI, and IVF on PTB compared to no treatment in subfertile women. Among linked births, 19% were born prior to 37 weeks completed gestation. After adjustment for maternal age, paternal age, maternal education, annual income, religious affiliation, female or male fertility diagnosis, and duration of subfertility, the odds of having a PTB were 2.2 times higher (95% CI 1.0-4.8) for women who conceived using ovulation drugs, 3.2 times higher (95% CI 1.4-7.2) for women who conceived using IUI and 4.2 times higher (95% CI 2.1-8.8) for women who conceived by IVF, compared to women with subfertility who used no treatment during the month of conception. Duration of pregnancy attempt was not independently associated with PTB. A reported diagnosis of female factor infertility increased the adjusted odds of having a PTB was 3.0 times higher (95% CI 1.5-6.0) compared to women who did not report any female factor infertility. Although slightly attenuated when excluding women with tubal factor, the odds of PTB were still significant (aOR 2.75; 95% CI 1.42-5.31) for women with any female factor infertility. Only 6.6% of the births conceived without any treatment during the month of conception were twins, and for OS this increased to 19% twins and 6% triplets, IUI births were 10.9% twins and 5% triplets, and IVF births were 30% twins and 2% triplets. Multiple

gestations had the highest association with adverse neonatal outcomes (aOR 28.0; 95% CI 15.6-68.6) when controlling for all other variables. In restricting analyses to singleton gestation, odds ratios remained elevated but were no longer significant for any type of treatment. However, female factor infertility was found to be independently associated with PTB when controlling for treatment, multiple gestations, and other potential confounders.

5.2 Clinical Implications and Recommendations

The findings from Aim 1 highlight the value of taking a detailed attempt history using a date-based approach. The fact that women who experienced a pregnancy (regardless of live birth) were better at recalling attempt duration supports the use of a life event history framework.[14] The findings of this research also caution against assuming that biological TARP is equivalent to what is commonly referred to as "trying to conceive," which is imbued with intentionality, or that either of these measures can be determined using a single question. In 2013, The Practice Committee of the American Society for Reproductive Medicine updated the definition of subfertility to include the phrase "12 months or more of **appropriately timed** unprotected intercourse or therapeutic donor insemination." This should be incorporated into questions assessing pregnancy attempt duration. Variations can cause bias in self-reports of time trying to conceive, skew fertility prognosis, and alter treatment plans. Physicians, in primary care and specialty settings, should avoid the use of a single question when assessing how long a couple has been having regular unprotected intercourse. Detailed attempt histories should be used to capture a more accurate and complete picture of "time trying to

conceive," including reports of the number of cycles using "fertility focused intercourse." Providers should also understand the potential impact of inaccurate pregnancy attempt reporting on patient treatment recommendations, which can unnecessarily increase patient's risk for undergoing potentially unnecessary treatments, which increase costs and may put them at risk for adverse perinatal outcomes.

Aim 2 demonstrated the necessity for providers to complete a full intervention inventory in addition to medical history with patients at all clinical encounters. Having a more complete picture of the things that women are doing either on their own or with CAM practitioners or other medical providers can improve treatment precision. Providers need to acknowledge that more likely than not their patients are engaging in nonmedical interventions with the intention of enhancing their fertility, but without adequate counseling women may be using approaches that could have opposing effects on treatments. Women who have been trying for longer are also more likely to engage in more interventions and should be asked to report on the things they may have tried over the years. The use of an intervention checklist to assess what nonmedical interventions patients are using has the potential to create open communication between patients and specialty providers by removing stigma surrounding nonmedical CAM and ensuring that providers have the most complete clinical picture when treating individual cases. This may also be an opportunity to ensure that their long durations of "regular, unprotected intercourse" also included at least 12 cycles of appropriate fertility-focus intercourse. These interactions with patients who are struggling to conceive is an ideal opportunity to discuss preconception care including the use of prenatal vitamins and achieving a healthy prepregnancy weight.

Findings from aim 3 suggest that women who are experiencing difficulty conceiving should consider first the opportunity for conception with less invasive treatments or no treatment. Providers should support this through disclosure of known risk and benefits for all treatment types. Although the time to conception may be longer, the potential for improved optimal birth outcomes should be weighed strongly against the desire to conceive faster. Clinicians should modify the practice of all fertility treatments to minimize incidence of multiple gestation, using OS methods with lower risk of superovulation, and single embryo transfer when providing IVF. Additionally, increased vigilance should be practiced during prenatal care for all women with subfertility, regardless of treatment received.

5.3 Future Directions

Each of the aims successfully answered the objectives at hand yet there is still need for additional research to solidify these findings. There is a need to conduct prospective research assessing biological time at risk for pregnancy, pregnancy attempt duration where a couples is explicitly intending to conceive, and behavioral "active" attempt or cycles of fertility focused intercourse. The potential for recall error is substantial in retrospective research and has to be acknowledged as a limitation of the research presented here. A prospective study would allow for a true gold standard of biological time at risk among a preconception cohort.

Research should also be conducted to evaluate cumulative pregnancy rates and neonatal outcomes when fertility treatment is delayed until couples meet the 12 cycles of appropriately timed intercourse rather than using the more subjective measures of 12

months of regular unprotected intercourse.

Aim 2 provided a glimpse into what nonmedical and behavioral interventions are being used in a population that may or may not have seen any specialty providers for difficulty conceiving. The study was limited by small numbers of women using some of the interventions, including partner-focused interventions. A larger prospective trial should be conducted to assess if nonmedical CAM, or behavioral interventions for both male and female partners, have any meaningful effect on conception in populations of subfertile couples.

Aim 3 found a direct effect of all types fertility treatment on the risk of preterm birth. Research on the non-ART approaches would be more feasible if universally there were improved surveillance of all fertility treatments (including less invasive OS and IUI). The findings were consistent with previously published research in identifying an increased risk on preterm birth, and future research should consider potential preconception or prenatal interventions that may prevent preterm birth among these higher risk populations of subfertile women conceiving using any fertility treatments.