BARRIERS TO AND FACILITATORS OF INFERTILITY MEDICATION ADHERENCE: A MIXED METHODS STUDY

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DOCTOR OF PHILOSOPHY

by
DIANE MAHONEY

B.S.N., University of Kansas, 1995
M.S.N., University of Kansas, 2000
D.N.P., University of Missouri-Kansas City, 2011

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BARRIERS TO AND FACILITATORS OF INFERTILITY MEDICATION ADHERENCE: A MIXED METHODS STUDY

Diane Mahoney, Candidate for the Doctor of Philosophy Degree

University of Missouri-Kansas City, 2019

ABSTRACT

Background. Infertility treatment protocols require women to engage in self-management of their prescribed medication regimens, yet adherence to infertility medication schedules have been suboptimal. No prior research has investigated barriers to and facilitators of infertility medication adherence (MA) that could assist in the development of effective interventions to overcome medication non-adherence (MNA).

Purpose. The purpose of this study was to assess barriers to and facilitators of infertility MA among women undergoing infertility treatment. This study was approved by the University of Missouri-Kansas City Institutional Review Board (IRB) and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting. The study setting was a reproductive medicine and infertility clinical practice serving women who reside in urban, suburban, and rural communities.

Methods. Supported by Ajzen and Fishbein's Reasoned Action Model, a convergent mixed methods design was conducted to correlate women's perceived barriers to and facilitators of infertility MA. Women in a convenience sample were interviewed and completed questionnaires at study onset followed by one to two subsequent months of

electronically monitored medication-taking using the Medication Event Management System® (MEMS).

Results. The total sample consisted of 30 participants, of which 18 (60%) participants used the MEMS® with infertility medication-taking. The overall median infertility adherence MA score was 0.98 with a range of .75 to 1.00. The median adherence score of women who were considered non-adherent (n=9) was 0.90, and those who were considered adherent (n=9) was 1.00. MA scores significantly ($r = -.49$, $p= 0.020$) increased when the total MA barrier scores decreased. Women with a higher MA total barrier scores had significantly ($p= 0.019$) lower MA scores compared to women with lower total barrier scores. Women who were adherent to their infertility medication regimen had a significantly ($p= 0.009$) higher probability to report a positive view on treatment success compared to women who were not adherent. Women who lived in urban and rural communities had a significantly ($p= 0.010$) higher probability to report a positive view regarding treatment success compared to women who lived in suburban communities. Caucasian and African-American women had a significantly ($p= 0.049$) higher probability to report feelings of self-blame for experiencing infertility compared to Asian, Hispanic, and Native American women. Women who had experienced two to three prior failed treatment cycles had a significantly ($p= 0.047$) higher probability to report feelings of emotional distress compared to women who had experienced zero to one prior failed cycle. Women with children had a significantly ($p= 0.015$) lower probability to report having a supportive partner compared to women who were childless. There were no significant relationships found between the reported MA facilitators and infertility MA scores.

Conclusion. These study findings offer new insight about this unique population that could impact the future of clinical practice. This study serves as a framework to foster ongoing scientific discovery including new interventional studies aimed at optimizing infertility MA.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Nursing and Health Studies, have examined a dissertation titled "Barriers to and Facilitators of Infertility Medication Adherence: A Mixed Methods Study," presented by Diane Mahoney, candidate for the Doctor of Philosophy degree and hereby certify that in their opinion it is worthy of acceptance.

Supervisory Committee

Cynthia L. Russell, Ph.D., RN, FAAN, Committee Chair
UMKC School of Nursing and Health Studies

Maryann Bozzette, Ph.D., RN
University of Missouri - St. Louis College of Nursing

Eduardo Abreu, M.D., DEng
UMKC School of Nursing and Health Studies

Sangbeak Ye, Ph.D.
UMKC School of Nursing and Health Studies

An-Lin Cheng, Ph.D.
UMKC School of Medicine

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CHAPTER 1

INTRODUCTION

Infertility is a condition that impacts 16% of reproductive aged women in the United States, and many women undergo infertility treatment in an attempt to become pregnant (Chandra, Copen, & Stephen, 2014; Thoma et al., 2013). Infertility treatment protocols require women to engage in self-management of their prescribed medication regimens, yet adherence to infertility medication schedules has been suboptimal, with medication non-adherence (MNA) rates ranging widely from 19% to 74% (Kruse, Eggert-Kruse, Rampmaier, Runnebaum, & Weber, 1990, 1991, 1993; Li, He, Yang, Yin, & Xu, 2011; McGovern et al., 2008). Infertility treatment regimens are complex, cycle-based (one treatment plan per cycle) and can impede women's daily lives (Boivin et al., 2012; Wu, Elliot, Katz, & Smith, 2013). Treatment cycles can incorporate multiple oral and/or injectable medications. Medication schedules range from daily to multiple daily dosing that is very time sensitive (Smith, Grimm, & Schwegel, 2012). Women with infertility are challenged by physical, psychological, emotional, and financial demands that can accompany treatment (Brod, Verhaak, Wiebinga, Gerris, & Hoomans, 2009). Still, researchers have not established a systematic process to monitor or improve medication adherence (MA) supported by a theoretical foundation. Failure to correctly take the medication during a treatment cycle decreases the likelihood of the medication having its intended effect on reproductive hormones, ovarian follicular development, and pregnancy, thus ultimately driving up healthcare costs for repeated treatments (Katz et al., 2011; Noorhasan, McCulloh, Cho, & McGovern, 2008). The cost per successful pregnancy and birth for all women who undergo cycle-based treatment is over $48,000 (Katz et al., 2011).

Adherence can be defined as "the extent to which a person's behavior—medication taking, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider" (Sabaté & World Health Organization, 2003, p. 3). Medication adherence is the degree to which individuals take their medications as prescribed and consists of three important components that include initiation, implementation, and discontinuation (Vrijens et al., 2012). Initiation occurs when the individual takes the first prescribed medication dose. Implementation is the extent to which the individual's actual dosing behaviors align with the prescribed dosing regimen (Vrijens et al., 2012). Discontinuation designates the time-point for which the next dose to be taken is omitted and medication-taking subsides (Vrijens et al., 2012). MNA occurs with late initiation, suboptimal implementation, and/or early discontinuation of prescribed medication regimens (Vrijens et al., 2012).

While MA intervention research has identified, compared, and improved health outcomes across acute and chronic populations, women undergoing infertility treatment have not been the population of focus although background factors such as age, race, education, income, and health insurance status have influenced medication-taking behaviors in other patient populations (Conn et at., 2015; Conn, Ruppar, Enriquez, & Cooper, 2015; Kilgore, Pulungan, Teigland, & Parente, 2016; Park, Howie-Esquivel, & Dracup, 2014; Whittle et al., 2016).

Thus, examining women's perceptions regarding barriers to and facilitators of infertility MA will address an important knowledge gap in reproduction science research pivotal to generating possible solutions for overcoming MNA (Mahoney, 2018). This study incorporated a mixed-methods design to generate a comprehensive understanding of barriers

and facilitators that influence MA in this patient population. Study findings will serve as a first step to provide important information for developing innovative interventions to significantly improve MA behaviors and reduce unnecessary health care expenditure for infertility services.

The intent of the mixed methods design was to merge quantitative and qualitative data in order to generate broader insight concerning barriers to and facilitators of infertility MA by incorporating multiple perspectives (Creswell, 2015). The quantitative methods included questionnaires to assess barriers to MA and background (demographic) factors, and electronic monitoring of MA using the MEMS® (MEMS Track Cap; Westrock Switzerland) to assess MA behaviors. Although there is no gold standard measure of MA, electronic monitoring is considered by many investigators to be the best method available. MEMS® can accurately record medication-taking and make clear distinctions between the phases of MA—initiation, implementation, and discontinuation. This is done by integrating a small microcircuit into the MEMS® specialized bottle caps in such a way that the microcircuit records the time and date when medication doses are removed from the bottle. Electronic monitoring has been used to assess adherence behaviors in many clinical trials (Vrijens & Urquhart, 2012). The qualitative methods included conducting participant interviews to capture women's perceived facilitators of MA and their personal experiences with infertility treatment.

Study Purpose and Working Hypothesis

The purpose of this study was to identify perceived barriers to and facilitators of MA among women undergoing infertility treatment using a dynamic approach. This study was intended to advance human reproduction research and scientific ingenuity by generating

valuable information necessary to design and test innovative, cost-effective behavior change interventions to overcome infertility MNA at a time when expanding affordable health care access for infertility services has become a nationwide initiative. Following are specific aims, research questions, and working hypotheses of the study.

Specific Aims, Research Questions, and Hypotheses

Primary Aim/Research Question

Primary Specific Aim: To identify barriers of and facilitators to MA among women undergoing infertility treatment.

Primary Research Question: What do women undergoing infertility treatment perceive as barriers to and facilitators of MA that influence their medication-taking behaviors?

Hypothesis 1. Women with a greater number of perceived barriers will demonstrate lower infertility MA scores than women with a lesser number of perceived barriers.

Hypothesis 2. Women with a greater number of perceived facilitators will demonstrate higher adherence scores than women with a lesser number of perceived facilitators.

Hypothesis 3. Differences will exist among perceived barriers and facilitators between women who are adherent and non-adherent.

Secondary Aim/Research Question

Secondary Specific Aim: To determine how background factors and personal experiences with infertility treatment influence women's infertility medication-taking behaviors.

Secondary Research Question: What background factors and personal experiences with infertility treatment are associated perceived barriers of and facilitators to MA among women undergoing infertility treatment?

Hypothesis 4. Differences will exist in women's personal experiences with infertility treatment based on women's age, race/ethnicity, level of education, income, and infertility insurance status.

Hypothesis 5. Differences will exist between women who are adherent and non-adherent by age, race/ethnicity, level of education, income, and infertility insurance status.

CHAPTER 2

REVIEW OF LITERATURE

Chapter two represents a systematic review accepted for publication. *Medication Adherence Among Women Undergoing Infertility Treatment: A Systematic Review* to be published in *International Journal of Women's Health and Reproduction Sciences* (Mahoney, Russell, & Cheng, 2019).

The reference list from this systematic review is incorporated into the references for the entire dissertation.

Abstract

Objectives: To investigate what is known regarding medication adherence in women undergoing infertility treatment.

Materials and Methods: The data bases PubMed (1940 to 2017), Embase (1980 to 2017), CINAHL (1982 to 2017), PsychINFO (1806 to 2017), and ProQuest dissertations were searched. Inclusion criteria were English-language: (1) prospective, (2) retrospective, (3) observational, (4) cross-sectional, (5) quasi-experimental, and (6) randomized controlled trial studies with medication adherence as a primary or secondary outcome in women with a diagnosis of infertility. Critical appraisal for study quality was assessed using Downs and Black Quality Checklist and STROBE guidelines.

Results: Three articles from 1993 to 2011 were analyzed. Sample sizes varied from 30 to 626 subjects with mean oral medication adherence rates ranging from 26% to 81% when used as first-line therapy. More frequent daily dosing was associated with lower adherence rates. Adherence was significantly lower when women were concerned about having side effects or reported three or more side effects versus one or two. Women with a

body mass index of <23 kg/m² or those who viewed medical treatment as convenient had higher adherence rates. None of the studies assessed medication adherence during controlled ovarian hyperstimulation (COH) cycles in conjunction with intrauterine insemination (IUI) or in vitro fertilization (IVF).

Conclusions: Oral medication adherence rates are suboptimal when used alone as first-line therapy. Further investigation of medication-taking behaviors is warranted in future research trials involving injection medications and COH cycles associated with IUI and IVF cycles to strengthen clinical practice.

Medication Adherence Among Women Undergoing Infertility Treatment:

A Systematic Review

Introduction

Infertility is a significant health problem for women, estimated to affect 80 million people worldwide (Rubin & Phillips, 2012; Sharma, Biedenharn, Fedor, & Agarwal, 2013). In the United States (U.S.), approximately 16% of women of childbearing age are affected by infertility (Thoma et al., 2013). Many women undergo infertility treatment and are highly motivated to become pregnant (Chandra et al., 2014). Infertility treatment incorporates a variety of modalities to help women achieve pregnancy from minimally invasive to highly invasive procedures in conjunction with fertility medication. Treatment regimens can incorporate oral and/or injection medication for controlled ovarian hyperstimulation (COH) in combination with or without intrauterine insemination (IUI), as well as assisted reproductive technology (ART) procedures such as vitro fertilization (IVF) (American Society for Reproductive Medicine [ASRM], 2012b).

Women who opt to undergo any sort of infertility treatment are advised by healthcare providers to engage in self-managed lifestyle behaviors (e.g., healthy diet, adequate physical activity, smoking cessation, marijuana cessation, alcohol restrictions) and to follow prescribed fertility medication protocols to increase the chances of treatment success (Alvarez, 2015; Hassan & Killick, 2004; Klonoff-Cohen, 2005; Nafisehsadat, Kazemi, & Hasanzadeh. 2014; Rooney & Domar, 2014). Yet, adherence to health provider recommended lifestyle changes has been problematic (Domar, Conboy, Denardo-Roney, & Rooney, 2012; Domar, Rooney, Milstein, & Conboy, 2015; Gormack et al., 2015; Rooney & Domar, 2018; Schilling, Toth, Rösner, Strowitzki, & Wischmann, 2012). In fact, negative lifestyle behaviors have contributed to lower pregnancy rates for women undergoing IVF (Kasum et al., 2017; Klonoff-Cohen, Lam-Kruglick, & Gonzalez, 2003; Klonoff-Cohen, Natarajan, & Chen, 2006; Klonoff-Cohen, Natarajan, Marrs, & Yee, 2001; Rittenberg et al., 2011; Rossi et al., 2011). This raises concerns regarding the extent to which women adhere to fertility medications while receiving treatment.

Adherence to prescribed medication is important for achieving targeted health outcomes (Vrijens et al., 2012). Medication non-adherence is recognized as a prevalent global problem in the general population, with adherence rates averaging 50% worldwide (Sabaté & World Health Organization, 2003). Nonetheless, the medication-taking behavior of women receiving infertility treatment has not been adequately assessed. This may be due to a belief that medication adherence is optimal in this patient population, particularly with high stakes procedures like IVF. After all, infertility treatment has resulted in successful pregnancies for many women, though most often after repeated treatments. While a woman's likelihood of pregnancy with infertility treatment decreases as she ages (35 years

and older), younger women (under 35 years) undergoing ART in the U.S. average 38% pregnancy rates for each treatment cycle (National Center for Chronic Disease Prevention and Health Promotion, 2017; Society of Assisted Reproductive Technology, 2016). Infertility treatment regimens are often complex and can impede women's daily lives (Boivin et al., 2012). Treatment cycles incorporate oral and/or injection routes. Medication schedules range from daily to multiple daily doses that are very time sensitive in nature (Smith, Grimm, & Schwegel, 2012). Failure to correctly take the medication during a treatment cycle decreases the likelihood of the medication having its intended effect on reproductive hormones and ovarian follicular development, ultimately driving up healthcare costs for repeated treatments (Katz et al., 2011; Noorhasan et al., 2008).

Adherence can be defined as "the extent to which a person's behavior—medication taking, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider" (Sabaté & World Health Organization, 2003, p. 3). In infertility literature, medication adherence is not well defined during non-ART cycles such as IUI. With respect to ART, adherence has referred to the continuation of ART cycles (including medication adherence) recommended by the infertility provider until pregnancy is attained or until there are provider recommendations to discontinue treatment (Gameiro, Verhaak, Kremer, & Boivin, 2013). Therefore, existing research has concentrated on ART cycle discontinuation rates rather than medication-taking patterns (Gameiro, Boivin, Peronace, & Verhaak, 2012; Gameiro et al., 2013).

Medication adherence has three distinct components: initiation, implementation, and discontinuation (Vrijens et al., 2012). Initiation is when a patient takes the first dose of a prescribed medication. Implementation refers to the degree to which the patient's actual

medication usage corresponds to the prescribed medication regimen. Discontinuation occurs when the next scheduled dose to be taken is omitted and no more medication is taken after this point. Thus non-adherence occurs with late or no initiation of the prescribed medication, suboptimal implementation of the prescribed regimen, or early discontinuation (Vrijens et al., 2012).

Women with infertility are a population challenged by physical, psychological, emotional, and financial demands that accompany treatment, and some women have reported taking fertility medication incorrectly (Brod et al., 2009; Huisman, Raymakers, & Hoomans, 2009; Markle, King, Martin, Kutteh, & Ke, 2002; Noorhasan et al., 2008). Yet, researchers have not established a methodological process to monitor medication adherence with this group of women. Nor has there been attention directed to factors to improve medication-taking behaviors in this population. Moreover, no prior review has explored the medication adherence patterns of women undergoing any type of infertility treatment. The aim of this review is to determine medication adherence rates in women undergoing assistive reproductive treatment. Study questions include: (1) What are fertility medication adherence rates? and (2) What are the predictors of and barriers to medication adherence among women receiving infertility treatment? Through identifying patterns, predictors, and barriers related to medication adherence in women with infertility, clinical interventions can be strengthened. By improving the quality of future medication adherence research, treatment clinical outcomes could be improved, further decreasing the likelihood of repeated failed cycles for non-adherence while ultimately reducing overall health care expenditure.

Methods

Literature Search Strategy

The systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) standards (Moher, Liberati, Tetzlaff, & Altman, 2009). A search was conducted to identify studies in which medication adherence among infertile women undergoing infertility treatment was investigated using PubMed (1940 to 2017), Embase (1980 to 2017), Cumulative Index of Nursing and Allied Health Literature (CINAHL) (1982 to 2017), PscyhINFO (1806 to 2017), and ProQuest dissertations. Combinations of the following terms were used: "adherence," "compliance," "persistence," "concordance," "non-adherence," "non-adherence," "noncompliance," "non-compliance," "infertil*," "fertil*," "subfertil*," "infecund*," "subfecund*," "barren," "sterility," "infertility treatment," "fertility treatment," "in vitro fertilization," "intrauterine insemination," "pharmaceutic*," "prescript*," "medicat*," "medicine," "medicines," "drug," "drugs," "women," "woman," and "female."

Inclusion/Exclusion Criteria

Inclusion criteria were: (1) prospective, retrospective, observational, cross-sectional, quasi-experimental, and randomized controlled trial studies; (2) female participants aged 18 to 44 years with a diagnosis of infertility documented in the medical record; and (3) medication adherence as the primary or secondary study outcome. Participants age 18 to 44 were included because this age range is representative of women who seek infertility treatment (Chandra et al., 2014). Participants younger than age 18 were excluded because they are not a population that seeks infertility services. Participants beyond the age of 44 were excluded because reproductive potential is reduced with advancing age (ASRM,

2012a). Studies were also excluded also if they were not published in the English language. The PRISMA Flow Diagram for the study selection process is displayed in Figure 2.1. Formal approval by an ethical review committee was not required by the university to conduct this review.

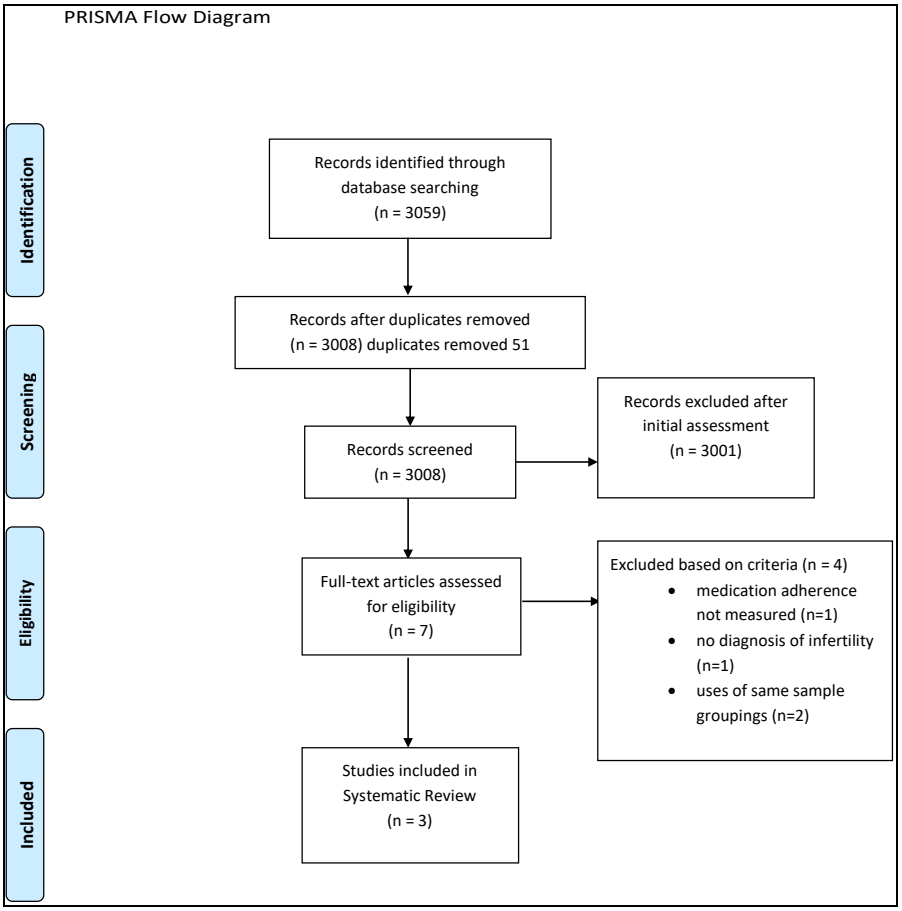


Figure 2.1 PRISMA 2009 Flow Diagram

Data Extraction

Data extraction was performed and agreed upon by two independent reviewers (DM and CR) using a structured data collection sheet. Data extraction included author/year/design, purpose, sample/setting, intervention, measures, results, strengths, and limitations. A summary of data extraction is presented in Table 2.1.

Quality Assessment

Critical appraisal was assessed by two independent reviewers (DM and CR) using the Downs and Black (1998) checklist for assessing methodological quality of randomized and non-randomized studies and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2008). The STROBE guidelines were used to assess the quality of one study (Li et al., 2011) because the Downs and Black (1998) criteria were not applicable for non-interventional studies. After discussion, there was complete agreement on study quality between both reviewers. The Downs and Black (1998) quality checklist consists of 26 items spread across five subscales including (1) reporting (9 items), (2) external validity (3 items), (3) bias (7 items), (4) confounding (6 items), and (5) power (1 item). Items are scored individually with a maximum total score of 32 indicating highest quality. This tool has demonstrated high internal consistency (Kuder-Richardson test = 0.89), good test-retest reliability (0.88), good criterion validity (0.89), and inter-rater reliability (0.75) (Downs & Black, 1998). STROBE guidelines are designed as criteria for reporting observational studies; however, these guidelines have been used to assess methodological rigor of published studies (Matteson & Russell, 2013). Quality reporting of the individual studies included in this review is shown in Tables 2.2 and 2.3.

Results

Five studies, published from 1990 to 2011, met the inclusion criteria. However, two of the five studies were excluded after three studies, conducted by the same authors (Kruse et al., 1990, 1991, 1993) revealed strong similarities of sample characteristics (e.g., age, years of infertility, study location, intervention, authors), raising suspicion of possible analysis of the same sample. Therefore, only results from the most recent study of these

three (Kruse et al., 1993) was used in this review analysis to ensure validity of study findings. The two earlier studies (Kruse et al., 1990, 1991) are shaded in Table 2.1 and were not included as individual study contributors in the analysis.

Table 2.1

Summary of Extraction Data

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
Li, He, Yang, Yin, and Xu (2011). Prospective, nonrandomized, observational, cross-sectional	Investigate the medication compliance of infertile patients with Polycystic Ovarian Syndrome (PCOS). Assess factors that might contribute to noncompliance in order to provide a basis for clinical treatment, specialist consultation, and health education.	N= 90 Age: x=28.71± 3.63 years 20-25 (n=17) 26-30 (n=45) ≥31 (n=28) BMI: x=24.0±4.34 kg/m² <23 (n=38, 23-25 (n=18), ≥ 25 (n=34) Race or ethnic group: NR Length of time attempting to conceive: ≥ 1 year No history of pregnancy: 68.9% Prior history of infertility treatment: 34.4%	None	1) Questionnaire consisting of 3 questions derived from the Morisky-Green test and 1 question addressing weight loss based on the principles of PCOS. 2) Questionnaire with contents assessing (a) demographic information, (b) disease diagnostic information, and (c) self-factors including personal, medical, economic, and social experiences and concerns	Primary findings: Overall compliance to treatment: 23 (25.6%) Compliance to medications: contraceptive drugs-31 (48.4%), anti-insulin resistance drugs-28 (52.8%), clomiphene-15(60%), traditional Chinese medicine-3(30%). BMI (P=0.040), convenience of medical treatment (P=0.012), and concerns about adverse drug effects (P=0.043) significantly affected compliance to treatment. Secondary findings: NR	Strengths: Sample inclusion criteria clearly specified, moderate sample size. Adherence measures adequately described. Statistical methods appropriate. Limitations: External review of study by an ethics review board not reported. Actual compliance rates not reported, only categorized as good compliance rates. Convenience sampling and nonrandomized. Race/ethnicity of sample not reported. Potential for sampling bias and sampling homogeneity limiting generalizability of study results. . Potential for a lower reliability and accuracy in participant self-reporting on survey questionnaires. Potential for inaccuracy in content validity on second questionnaire. No theoretical framework basis addressed.

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
		Self-pay for medical expenses: 88.9% Postsecondary education: 57.8% Setting: Reproductive Medical Center in China		surrounding PCOS. Timing: baseline, study lasted for 6 months		
McGovern et al. (2008). Retrospective, randomized controlled trial	Examine mediation adherence in the metformin-containing arms of the primary study to determine whether participants within the expected range for similar trials.	N=626 metformin group: n=208, clomiphene group: n=209, combination group: n=209 Age (years): metformin group 28.1± 4.0, clomiphene group 27.9± 4.0, combination group 28.3 ± 4.0 BMI: metformin group 35.6 kg/m² ± 8.5, clomiphene group 36.0± 8.9, combination group 34.2 ± 8.4	Metformin Group: 2000mg daily plus clomiphene placebo Clomiphene Group: 50, 100, or 150 mg daily for 5 days per cycle plus metformin placebo. Combined Group: metformin 2000mg daily plus clomiphene 50, 100, or 150 mg	Pill counts used to assess adherence by percentage of recommended tablets not in the returned bottles by counting the remaining tablets. Timing: baseline and monthly for up 6 cycles or 6 months, pill counts from returned bottles performed monthly.	Primary findings: Overall median adherence rate was 81%. Median adherence rates were 81.6% in metformin group and 81.7% in combination group. No significant (P=0.80) difference in medication adherence between metformin group and combined group. Ovulatory rates were low in the metformin group across all levels of adherence. Secondary findings: Median	Strength: Sample randomization and control, and blinding present, Sample large and heterogeneous. Sampling bias minimized by stratification according to the study site and the presence or absence of previous exposure to either of the study drugs. Instruments were adequately described. Statistical methods appropriate. Limitations: Study setting not adequately described. A total of 176 participants dropped of study. Medication adherence not originally reported in primary study. Discrepancy between sample size of metformin arm (n=195) in secondary study

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
		Race or ethnic group: Metformin group-Caucasian 67.6%, Hispanic 29.3%, Black 19.3%, Asian 2.4%, Native American 13.0%: Clomiphene group-Caucasian 70.7%, Hispanic 25.4%, Black 17.8%, Asian 2.4%, Native American 10.1%; Combination group-Caucasian 71.2%, Hispanic 23.9%, Black 15.4%, Asian 3.4%, Native American 11.5% Length of time attempting to conceive (months): metformin group 39.0± 31.9, clomiphene group 41.4± 39.4,	daily for 5 days per cycle.		adherence for clomiphene group was 100% in clomiphene and combined groups.	and sample size of metformin arm (n=208) reported in primary study. Pill counts less reliable in assessing medication adherence if participants removed pills out of bottle that were not taken. Primary study was not designed to investigate adherence systematically. No theoretical basis addressed.

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
		combination group 40.7 ± 36.0 Prior history of infertility treatment: metformin group 53.4%, clomiphene group 55.5%, combination group 55.5% Self-pay for medical expenses: NR Postsecondary education: NR Setting: Multi-centers, location unknown.				
Kruse, Eggert-Kruse, Rampmaier, Runnebaum, and Weber (1993). Prospective, cross-sectional, randomized	To examine the relationship between adverse reactions and patient compliance in women with primary infertility.	N=61 Age: x=30.4±4.4 years (range, 21-39 years) BMI: NR Race or ethnic group: NR Length of time attempting to conceive: 4.5± 2.7 years (range, 9 months-19 years)	Ethinylestra-diol at 40µg twice daily or 20µg four times daily for 7 days	Medication Event Monitoring System used to evaluate percentage of prescribed doses taken during the period. (administrative compliance-container openings recorded during the period	Primary findings: Overall mean compliance was 75.7%. Administration compliance ranged from 7-143% and regimen compliance ranged from 0-100% for twice a day dosing. Administration compliance ranged from 14-136% and regimen compliance ranged	Strengths, randomization present, moderate sample size. Adherence measures adequately described. Key variables were operationalized. Limitations: Limited review of literature to provide synthesis on the existing evidence of medication adherence. External review of study by an ethics review board not reported. Method

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
		No history of pregnancy: NR Self-pay for medical expenses: NR Postsecondary education: NR Setting: Infertility Unit of Women's Hospital, Heidelberg, Germany		divided by the prescribed number of doses during the period) and adherence to the prescribed dose schedule (regimen compliance-the number of days in which two openings for twice daily regimen or four openings for four times per daily regimen) Timing: daily for 7 days Standardized questionnaire to assess for adverse drug reactions which asked participants to rate symptoms which they attributed to the drug as mild, moderate, or severe Timing: once after	from 0-100% for four times per day dosing. Mean administration compliance: 85% for twice a day dosing and 65% for four times per day dosing ($P<0.05$). Mean regimen compliance: 62% for twice a day dosing and 34% for four times per day dosing ($P<0.005$). No significant difference in compliance comparing participants with or without adverse drug reactions. Compliance was significantly lower ($P< 0.05$) when participants reported three or more adverse drug reactions versus one or two: 54% versus 84% in administrative	of sample randomization design not addressed. No report on avenues used to minimize sampling bias. Sample inclusion criteria not clearly specified. Limited sample demographics. Ethnicity not reported-potential of sample homogeneity. Potential for a lower reliability and accuracy in participant self-reporting on questionnaires. Statistical methods used were not adequately described. No theoretical framework basis addressed.

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
				completing 7 days of ethinylestradiol	compliance and 31% versus 58% in regimen compliance). Compliance was lower in participants with nausea and vomiting compared to those without these symptoms: 59% versus 91% in administrative compliance and 34% versus 66% in regimen compliance (P< 0.005). Compliance was lower with moderate or severe side effects compared to mild side effects: 48% versus 85% in administrative compliance and 25% versus 59% in regimen compliance (P< 0.005).	

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
Kruse, Eggert-Kruse, Rampmaier, Runnebaum, and Weber (1991). Prospective, cross-sectional, randomized	To investigate patient compliance with two different dosage schedules of ethinyloestradiol 20µg four times daily versus 40µg two times daily.	N=65 Age: x=29.9 years (range, 21-39 years) BMI: NR Race or ethnic group: NR Length of time attempting to conceive: 4.3 years (range 9 months to 19 years) No history of pregnancy: NR Self-pay for medical expenses: NR Postsecondary education: NR Setting: Infertility Unit of Women's Hospital, Heidelberg, Germany	Ethinyloestr-adiol at 40µg twice daily or 20µg four times daily for 7 days	Medication Event Monitoring System used to evaluate percentage of container openings (recorded pill openings during the period divided by the prescribed number of doses during the period multiplied by 100) and adherence to the prescribed dose schedule (regimen compliance-the number of days in which two openings for twice daily regimen or four openings for four times per daily regimen) Timing: daily for 7 days	Mean overall compliance was 75.7% (range 7.1 - 143%). Mean compliance with twice daily dosing was 85% compared to 67% with four times per day dosing ($P<0.05$) Regimen compliance: 63% for twice a day dosing and 36% for four times per day dosing ($P<0.005$).	Strengths, randomization present, moderate sample size. Adherence measures adequately described. Key variables were operationalized. To minimize attrition, participants who failed to return MEMS bottles were emailed reminders. Statistical methods appropriate. Limitations: Limited review of literature to provide synthesis on the existing evidence of medication adherence. External review of study by an ethics review board not reported. Method of sample randomization design not addressed. Sample inclusion criteria not clearly specified. No discussion of power analysis to estimate sample size. Limited sample demographics. Potential for limitation of study finding generalizability. Ethnicity not reported-potential of sample homogeneity. No theoretical framework basis addressed.

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
Kruse, Eggert-Kruse, Rampmaier, Runnebaum, and Weber (1990). Prospective, cross-sectional, randomized	To investigate patient compliance with ethinyl-oestradiol therapy of 20 µg four times daily.	N=30 Age: x=28.8 years (range, 21-36 years) BMI: NR Race or ethnic group: NR Length of time attempting to conceive: 3.9 years (range 9 months to 8 years) No history of pregnancy: NR Self-pay for medical expenses: NR Postsecondary education: NR Setting: Infertility Unit of University Women's Hospital	Ethinyl-oestradiol therapy of 20 µg four times daily.	Medication Event Monitoring System. Compliance data was obtained as listings of the time and date of individual bottle openings and closings, duration of openings, and the hours since previous dose. Compliance was defined as the number of doses taken during period divided by the number of prescribed doses during period multiplied by 100. Timing: daily for 7 days Interview regarding adverse drug effects which consisted of	Mean overall compliance was 64.9% (range 14.3 to 136%). Mean adherence to prescribed QID regimen was 34.3% (range 0-114%). Sixteen of the 30 participants reported adverse drug reaction on response open-question or spontaneously. Twenty-four participants reported side effects on standardized questionnaire. Seventy-nine percent of the symptoms were rated as being mild. In participants who had a compliance rate >65%, adherence rate correlated with reported adverse drug reactions	Strengths: randomization present. Adherence measures adequately described. Key variables were operationalized. Addressed accuracy of MEMS. To minimize attrition, participants who failed to return MEMS bottles were emailed reminders. All participants were interviewed by same investigator. To reduce confounding variables, only participants who were not taking other medications during study were included. Statistical methods appropriate. Limitations: Small sample size. Limited review of literature to provide synthesis on the existing evidence of medication adherence. External review of study by an ethics review board not reported. Method of sample randomization design not addressed. Sample inclusion criteria not clearly specified. No discussion of power analysis to estimate sample size. Limited sample demographics. Potential for limitation of study finding

Table continues

Author/Year/Design	Purpose	Sample/Setting	Intervention	Measures	Results	Strengths/Limitations
				one open question followed by a standardized questionnaire rating adverse symptoms as mild, moderate, or severe. Timing: Immediately after the 7-day ethinyl oestradiol regimen completed	inversely (r=0.71; P<0.01). The lower the compliance rate, the more adverse drug reactions were reported (no r or P value provided). Compliance was positively correlated with duration of infertility (r=0.44; P<0.05).	generalizability. Ethnicity not reported-potential of sample homogeneity. Potential for a lower reliability and accuracy in participant self-reporting on questionnaires. No theoretical framework basis addressed.

Table 2.2

Downs and Black Checklist

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	Quality Score
McGovern et al. (2008)	1	1	1	1	1	1	0	1	1	0	0	1	0	1	1	1	1	1	0	0	1	1	1	0	0	1	5	23
Kruse et al. (1993)	0	0	1	1	0	1	1	1	0	0	0	0	1	0	0	1	1	1	1	1	1	0	1	0	0	0	1	14

Key:
Reporting: "Yes=1," "No=0"
1. Is the hypothesis /aim /objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients / samples included in the study clearly described?
4. Are the interventions of interest clearly described? "Yes=2," "Partially=1", "No=0"
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? "Yes=1," "No=0"
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?

External validity: "Yes=1," "No=0," "Unable to determine=0"
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

Internal validity-bias: "Yes=1," "No=0," "Unable to determine=0"

14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dredging" was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/s reliable?
20.Were the main outcome measures used accurate (valid and reliable)?

Internal validity -confounding (selection bias): "Yes=1," "No=0," "Unable to determine=0"
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
23. Were study subjects randomized to intervention groups?
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?

Power
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%.
Size of smallest intervention group
1. A 1<n1 0
2. B n1-n2 1
3. C n3-n4 2
4. D n5-n6 3
5. E n7-n8 4
6. F n8+ 5

Table 2.3

STROBE Quality Assessment

	Item No	Recommendation	Li et al, (2011)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any pre-specified hypotheses	No
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Yes
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	No
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	No
Study size	10	Explain how the study size was arrived at	No
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	No
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes
		(*b*) Describe any methods used to examine subgroups and interactions	No
		(*c*) Explain how missing data were addressed	No
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	No
		(*e*) Describe any sensitivity analyses	No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Yes
		(b) Give reasons for non-participation at each stage	Yes
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	Yes

Table continues

	Item No	Recommendation	Li et al, (2011)
		(b) Indicate number of participants with missing data for each variable of interest	No
Outcome data	15*	Report numbers of outcome events or summary measures	Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes
		(*b*) Report category boundaries when continuous variables were categorized	No
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	No
Discussion			
Key results	18	Summarize key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalizability	21	Discuss the generalizability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No

Characteristics of Study Participants

The total sample size was 777 participants. Individual study sample sizes ranged from 30 to 626 subjects with mean ages ranging between 28 and 30 years. Only one study reported on participant race/ethnicity with the majority (68%) being of Caucasian ancestry (McGovern et al., 2008). Mean body mass index (BMI) ranged from 24.0 to 36.6 kg/m² (Li et al., 2011; McGovern et al., 2008). Length of time attempting to conceive varied from one year to more than four years (Kruse et al., 1993; Li et al., 2011). Most of the participants (n= 716) were infertile women with polycystic ovary syndrome (PCOS).

Study Location and Practice Setting

Studies were conducted in the United States (McGovern et al., 2008), Germany (Kruse et al., 1993), and China (Li et al., 2011). One study addressed the type of payment for services, reporting 88.9% of participants were self-pay (Li et al., 2011). In two studies, 34.4% to 55% had undergone prior infertility treatment, and 31.1% to 36.8% reported a previous pregnancy (Li et al., 2011; McGovern et al., 2008).

Study Purpose and Study Type

In all three studies, medication adherence was examined as first-line therapy. None of the studies assessed adherence associated with IUI or IVF cycles. Two of the three studies (Kruse et al., 1993; McGovern et al., 2008) shared a common purpose to examine oral medication adherence, while the remaining study (Li et al., 2011) evaluated the combination of adherence to oral medication and weight loss recommendations. One study (Li et al., 2011) was a prospective, observational design; one study (Kruse et al., 1993) was prospective and randomized without a control group; and the remaining study (McGovern et

al., 2008) was a randomized controlled trial with medication adherence examined retrospectively.

Medication Adherence and Theoretical Framework

Researchers in two of the three studies measured medication adherence using objective measures, which were medication event monitoring (Kruse et al., 1993) and pill counts (McGovern et al., 2008). The remaining study (Li et al., 2011) measured medication adherence using a subjective measure (brief medication questionnaire). Mean adherence rates ranged from 26% to 81% (Li et al., 2011 & McGovern et al., 2008). There was no reporting on specific types of non-adherence (e.g., initiation, execution, persistence). None of the studies used a supporting theoretical framework.

Predictors and Barriers Related to Medication Adherence

In two of three studies researchers investigated possible factors that contributed to treatment non-adherence (Kruse et al., 1993; Li et al., 2011). Medication adherence was significantly lower when participants were concerned about having side effects or reported three or more side effects versus one or two (Kruse et al., 1993; Li et al., 2011). Participants who had a BMI <23 kg/m² or who viewed medical treatment as convenient had higher adherence rates (Li et al., 2011). The more frequent the medication dosing per day, the lower the adherence rates (Kruse et al., 1993; Li et al., 2011; McGovern et al., 2008).

Discussion

As the first of its kind, this systematic review was conducted to investigate medication adherence among women undergoing infertility treatment. Only three studies met criteria for inclusion in this review. While an abundance of literature exists on adherence to lifestyle recommendations in women receiving infertility treatment, interest in

studies on medication-taking behaviors has been overlooked 4; Zarinara et al., 2016). This review revealed that first-line oral medication adherence rates have a wide variation (26% to 81%). None of the studies assessed injection medication adherence nor medication-taking patterns during COH cycles associated with IUI and IVF. One could assume that women taking first-line oral medications would not have as high stakes—time investment, financial commitment, medical risks—as women undergoing more advanced therapy, which could influence adherence behaviors. However, this review provided evidence that oral medication adherence rates are consistent with general adherence rates in the literature that average 50%.

One of the three studies in this review addressed a lifestyle factor combined with medication adherence behavior. Li and colleagues (2011) examined treatment adherence to oral medications and weight loss recommendations within a subpopulation of infertile, obese women with PCOS. Obesity is a lifestyle management factor known to reduce infertility treatment success, and this review found that women who were not obese demonstrated better oral medication adherence (Bellver, Busso, Pellicer, Remohí, & Simón, 2006; Pinborg et al., 2011; Rittenberg et al., 2011). Thus, obese women may be at higher risk for multiple non-adherence behaviors (Mutsaerts, Kuchenbecker, Mol, Land, & Hoek, 2013). A recent study showed that 40% of women seeking infertility treatment actively engaged in at least four unfavorable lifestyle-related behaviors that could negatively influence reproductive outcomes (Piché, Babineau, Robitaille, Lachance, & Ruchat, 2018). This novel systematic review has provided groundbreaking evidence that oral infertility medication adherence behaviors are also unfavorable. The combination of medication non-adherence and negative

lifestyle behaviors present a new conundrum that has not been adequately addressed in prior literature for this population.

Medication side effects and dosing frequency were observed as potential barriers to adherence (Kruse et al., 1993; Li et al., 2011, McGovern et al., 2008). Understanding potential barriers is important for optimizing adherence during infertility treatment cycles. As scientists continue to advance strategies for improving innovative reproductive procedures, technology can only be effective if medication protocols are followed. So far, the relationship between fertility medication non-adherence behaviors and reproductive outcomes (canceled cycles, clinical pregnancies, live birthrates) has not been well documented in the literature. Markle et al. (2002) found that failure of women to correctly self-administer injection medication resulted in lower pregnancy rates.

Adherence to injection medication was not measured in any of the studies from this review although these medications have been problematic for other patient populations such as diabetes and those with multiple sclerosis (Capoccia, Odegard, & Letassy, 2016; Giovannoni, Southam, & Waubant, 2012). Prescribed injectable regimens are commonly used in infertility treatment regimens. They are available in either single or multiple-dose vials requiring the client to withdraw the medication into a syringe prior to administration or administer preloaded, multiple-dose self-injection pens. Women have reported concerns about self-administering injections correctly (Brod et al., 2009; Huisman et al., 2009). Some women have made medication errors but failed to report them to the infertility nurse or physician due to either considering the error insignificant or fearing a negative reaction from the provider (Huisman et al., 2009). One study reported a case in which the client knowingly self-administered less than the prescribed dosage of injection medication in order to save on

medication cost (Noorhasan et al., 2008). The studies in this review did not examine women's perspectives on taking fertility medication. However, discrepancies between healthcare providers' and clients' perspectives on injection medication-taking behaviors have been explored. Providers reported concern about client adherence to self-injection medications, yet they were surprised to find that women were taking incorrect medications, administering incorrect doses, and self-injecting medication incorrectly (Boivin et al., 2012; Brod et al., 2009).

The infertility healthcare environment along with prescribed medication protocols seem to overwhelm women who undergo infertility treatment. Li et al. (2011) reported that women who viewed their infertility treatment as convenient demonstrated higher adherence rates compared to those who found the treatment inconvenient. Treatment burden has been an ongoing problem for this patient population (Boivin et al., 2012; Brod et al., 2009; Huisman, , 2009). In fact, the inconvenience of frequent medication injections and total length of treatment are central contributors to infertility treatment strain (Brod et al., 2009). In addition, the clinic environment has been shown to amplify treatment burden and impact women's decisions to end treatment. Factors reported by women include lack of continuity of care, negative health provider attitudes, ineffective communication with clinic staff, and insufficient time for questions (Boivin et al., 2012). A patient-centered care model has gained notable recognition as an indicator of high-quality infertility services (Aarts et al., 2012; Gameiro, Canavarro, & Boivin, 2013; Huppelschoten et al., 2015). Thus, understanding the relationship between quality of care and respective attitudes and behaviors toward medication adherence would prove noteworthy.

Experts have begun an initiative to identify avenues for overcoming barriers to infertility treatment by improving care for women both nationally and internationally (ASRM, 2015). The U.S. health insurance environment has been an obstacle to gaining coverage for infertility services (National Conference of State Legislatures, 2014). Only 15 states have passed laws that require insurers to either cover or offer coverage for infertility diagnosis and treatment, although some employers do provide infertility coverage in non-mandated states (National Conference of State Legislatures, 2014). The American Society for Reproductive Medicine released a white paper on the current state of patient access to fertility care in the U.S. which outlined steps to improve access to care that include infertility coverage (ASRM, 2015). As this initiative moves forward, the urgency to redirect the focus on barriers to medication adherence may become a greater priority.

The focus in the general medication adherence literature has been on interventions to improve quality of life, increase life expectancy, and reduce healthcare costs in chronic disease populations (Costa et al., 2015). In the U.S., medication non-adherence has been responsible for 125,000 deaths and is estimated to well exceed $100 billion in healthcare expenditures annually (Viswanathan et al., 2012). The average cost per successful pregnancy and birth for women who undergo cycle-based infertility treatment is over $48,000 (Katz et al., 2011). Non-adherence to fertility medication is usually not life-threatening, although fertility quality of life has been a concern (Boivin, Takefman, & Braverman, 2011). Women's perceptions about their infertility treatment experience has been associated with quality of life (Aarts et al., 2012). The relationship between fertility quality of life and medication adherence behaviors has not been established.

Strengths and Limitations

The unprecedented nature of the findings in this systematic review serves as a major strength by offering evidence that oral medication adherence, used as first-line fertility therapy, could be more problematic than previously assumed by clinicians and researchers. Two of the three studies used randomization into group assignment, which minimizes study bias and strengthens findings. Nonetheless, several limitations exist that must be scrutinized. First, studies not published in the English language were excluded, and studies published in other languages could have altered the results. Second, this review included a very small sample size, and most study subjects were a subpopulation of infertile women with PCOS, limiting generalizability of findings. Only three studies were included for this review after two studies were excluded secondary to suspicion of same sample groupings. Third, the studies were focused only on oral medications during first-line therapy and did not include injection medications nor medication adherence during IUI and IVF treatment cycles. Fourth, one study examined medication adherence retrospectively. Although retrospective studies help establish cause and effect relationships (contributory factors), interpretation of study findings is limited, particularly when both selection bias and recall bias are present. Fifth, different tools were used to measure medication adherence, which could potentially confound results and hinder study inferences.

Implications from the Findings

As initiatives are in motion to broaden access for infertility services, understanding medication-taking patterns will be important. Reproductive healthcare providers should reinforce the importance of following medication regimens. The validation of medication adherence in research trials involving assisted reproductive therapies will better inform,

cultivate, and perpetuate stronger innovative discoveries in reproduction science to strengthen clinical practice.

Recommendations for Future Research

Future investigations are needed exploring women's medication adherence patterns during IUI and IVF cycles. Insight on how healthcare delivery of infertility services (e.g., degree of patient-centeredness, healthcare team communication, availability of third-party reimbursement) impacts medication taking could reinforce continuity of care and consequently, medication adherence. The impact of infertility insurance coverage on medication adherence rates deserves further attention as healthcare costs continue to skyrocket. Determination of whether adherence rates differ by regions of mandated infertility insurance coverage would also be beneficial. The relationship between motivation to conceive and likelihood of adherence will be important if theory driven interventions are deemed necessary. Moreover, investigating how quality of life and environmental factors impact medication adherence will be important particularly when family support and treatment demands (e.g., psychological stress and anxiety, time off work for appointments, treatment costs) could affect decisions regarding continuation of services. Lastly, standardization of medication adherence tools is needed in future infertility research.

Conclusion

The study findings from this review confirm that fertility medication adherence research remains scarce. Additional research is timely and compelling. The state of the science on fertility medications is still underdeveloped when compared to the general medication adherence research. Aligning medication-taking behaviors with reproductive outcomes (i.e., canceled cycles, clinical pregnancies, live birthrates) during IUI and IVF

cycles in future studies will help determine if tailored interventions are indicated. Oral medication adherence rates are suboptimal when used alone as first-line therapy. Further investigation of medication-taking behaviors is warranted in future research trials involving injection medications and COH cycles associated with IUI and IVF cycles to strengthen clinical practice. Greater exploration into such unchartered territory will answer the call of scientific inquiry through fostering innovation and versatility to advance human reproduction science.

CHAPTER 3

THEORETICAL FRAMEWORK AND METHODOLOGY

Barriers of and Facilitators to Infertility Medication Adherence Study (B-NFORMED): A Mixed Methods Study was supported by theory. This study design was a convergent mixed methods design in which quantitative and qualitative data assessing barriers to and facilitators of infertility MA were collected simultaneously and correlated with 1-2 consecutive months of electronically monitored infertility MA behaviors. A mixed methods design was used to gain deeper insight concerning this matter and maximize strengths of both quantitative and qualitative designs.

Theoretical Framework

In a recent systematic review (Mahoney et al., 2019), it was found that no supporting theoretical framework was used to guide studies that investigated women's medication-taking behaviors while undergoing infertility treatment. The theoretical framework guiding the B-NFORMED study was the Reasoned Action Model (Fishbein & Ajzen, 2010).

Fishbein and Ajzen's Reasoned Action Model

Fishbein and Ajzen's Reasoned Action Model (2010), the most current theoretical formulation for predicting human social behavior, postulates that intention determines the likelihood of behavior performance. For more than 50 years, Drs. M. Fishbein and I. Ajzen have worked jointly and individually to refine their approach to predicting and changing behavior (Ajzen, 1985, 1988, 1991; Ajzen & Fishbein, 1969, 1970, 1977, 1980, 2000, 2004; Fishbein, 1963, 2003; Fishbein & Ajzen, 1974, 1975, 2005, 2010).

Evolution of the Reasoned Action Model

Fishbein's (1963) early expectancy-value model purported that behavioral beliefs about the likely outcome of performing a certain behavior directly influenced one's attitude about that behavior. Ajzen and Fishbein (1980) subsequently collaborated to explore attitudes, behaviors, and intentions, later formulating a theory known as the Theory of Reasoned Action (TRA). The TRA addressed the normative construct—acknowledging that normative beliefs were weighted by motivation to adhere to a behavior change— that was lacking in prior work (Ajzen & Fishbein, 1969, 1970, 1977, 1980; Fishbein & Ajzen, 1974, 1975).

Additionally, the TRA incorporated background factors that include demographic variables (e.g., age, gender, education, race) and individual differences (e.g., personality, mood, emotions) that were thought to indirectly influence one's behavioral beliefs and normative beliefs toward performing a certain behavior. Further, Ajzen (1985, 1988) introduced an additional construct, perceived behavioral control. In congruence with behavioral beliefs and normative beliefs within the TRA, control beliefs were proposed as a function of people's perception of their control over performing a behavior. This extension to the existing theory became known as the Theory of Planned Behavior (TPB) (Ajzen, 1988, 1991).

Meanwhile, responding to a national initiative to unify variables among major theories that guided HIV prevention research, Fishbein (2000) modified the theory by surmising the Integrative Model that further incorporated attitudes, perceived norms, and self-efficacy as functions of underlying beliefs about performing a specified behavior. Although both theorists continued to work independently, Fishbein's Integrative Model

(2000) shared similarities to Ajzen's (1991) TPB. Thus over time, the two theorists reunited to resolve differences between their models that resulted in the most current framework, the Reasoned Action Model (Fishbein & Ajzen, 2010).

Present Reasoned Action Model

Fishbein and Ajzen (2010) contended that people's beliefs about a behavior is assumed to regulate their intention to engage in that behavior. Intentions are indicative of one's willingness or readiness to implement a behavior (Fishbein & Ajzen, 2010). Beliefs about respective behaviors are derived from a host of background factors such as personal experiences, personality, income, religion, age, race/ethnicity, education, and family dynamics. Background differences between individuals are considered to influence how information is recalled and interpreted, which impacts beliefs (Fishbein & Capella, 2006). These beliefs that influence one's decision whether to perform a certain behavior have been categorized into three determinants of intention—behavioral beliefs, normative beliefs, and control beliefs (Fishbein & Ajzen, 2010; Fishbein & Capella, 2006).

Behavioral beliefs are assumed to regulate an individual's attitude toward performing a behavior. As such, one's attitude with respect to performing a behavior will be more or less favorable based on the extent to which performance of the behavior is perceived as positive versus negative. Normative beliefs are based on the extent to which important people in one's life would approve or disapprove of a behavior being performed. Thus, if a majority of important people are believed to approve of the behavior or actually performs the behavior themselves, the more likely the individual will perceive societal pressure to perform the behavior (Fishbein & Ajzen, 2010). Figure 3.1 shows a schematic

representation of the Reasoned Action Model. The Reasoned Action Model is also displayed in Appendix A.

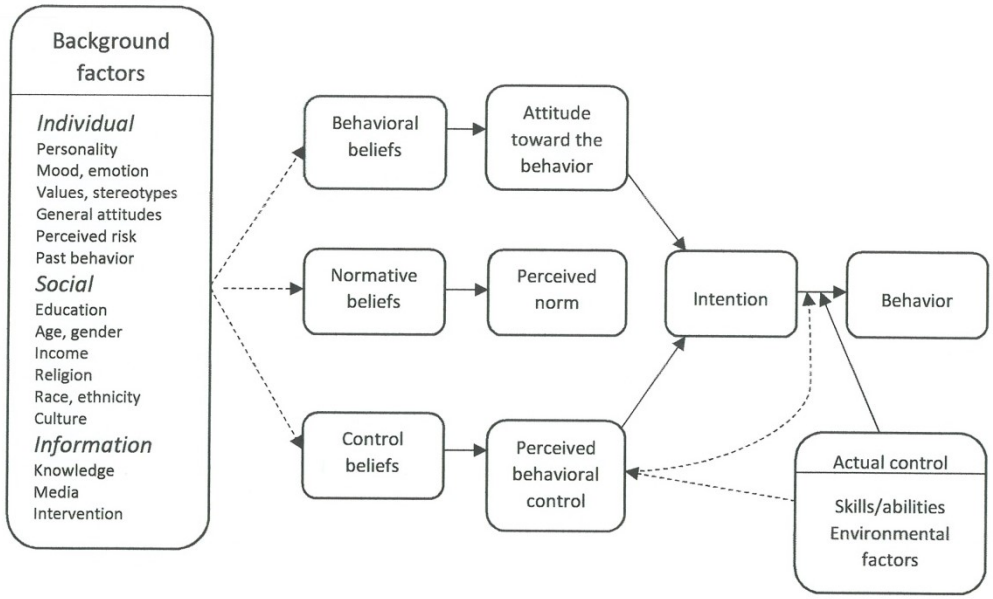


Figure 3.1. Fishbein and Ajzen's Reasoned Action Model (Fishbein & Ajzen, 2010)

The B-NFORMED study concentrated on (a) women's background factors and varying personal experiences with infertility treatment that could influence their beliefs about medication-taking, (b) behavioral beliefs that influence women's attitudes toward infertility medication-taking, (c) normative beliefs that originate from women's perceptions of social pressure from important persons that approve or disapprove of their decision to undergo infertility treatment, and (d) control beliefs (perceived barriers and facilitators) as determinants of behavioral intention that can impact women's likelihood of performing the behavior of interest, infertility MA. Control beliefs are perceived personal and environmental factors that inhibit or help the likelihood of performing a behavior (Fishbein & Ajzen, 2010). These beliefs determine one's self-efficacy or perceived behavioral

control—one's perception of the extent of barriers and facilitators that are present (Fishbein & Ajzen, 2010).

Perceived behavioral control moderates the effects of intentions on behavior. If more facilitators are perceived than barriers, one's level of perceived behavior control will be high. The stronger the intention to perform a behavior, the greater likelihood the behavior will be performed. Insufficient abilities, skills, and environmental constraints could realistically prevent an individual from acting on intention to perform, which is known as actual control. Collectively, a person's attitude about executing the behavior, perception of social pressure to perform a behavior, and perception of barriers to and facilitators of accomplishing a behavior leads to readiness to perform that behavior (Fishbein & Ajzen, 2010).

Methodology

The following is a description of the methodology used in the research design and participant recruitment. Setting for recruitment of participants, data collection methods, instrument selection, and psychometric properties are discussed. Lastly, study procedures and data management are presented.

Research Design

The Primary Investigator (PI) conducted a correlational, convergent mixed methods design in which quantitative and qualitative data were collected simultaneously and correlated with one to two consecutive months of electronically monitored infertility MA behaviors. A mixed methods approach was most suited to understand the complexities surrounding medication-taking patterns of women undergoing infertility treatment by generating richer data than either a quantitative or qualitative method alone (Johnson,

Onwuegbuzie, & Turner, 2007). Questionnaire data were collected at baseline on the study variables, MA barriers and background factors. Interview data were generated at baseline on the study variables, MA facilitators and personal experiences with infertility treatment. MA behaviors were documented by one to two months (one to two fertility treatment cycles) of electronic monitoring using MEMS®. MA barriers were measured using the Adherence Starts with Knowledge (ASK-20) Adherence Barrier Survey (Hahn et al., 2008). Background factors were assessed using a demographics questionnaire. MA facilitators and personal experiences with infertility treatment were measured by the PI via a structured interview. MA was measured using MEMS®.

Participants

The study population were women undergoing infertility treatment. The RRC patient volume was sufficient to recruit a convenience sample of 30 participants in the study timeframe. A recent study (Atsuta et al., 2017) revealed a correlation (r) of -0.51 between mean ASK-20 Adherence Barrier Survey total scores and MA scores, which represents a large effect (r^2= .26) based on Cohen's (1988) criteria for evaluating effect size measured by r^2.Thus a power analysis using the G*Power 3 computer program (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that a total sample size of 27 was needed to a detect a minimum correlation of 0.51 with 80% power using a t-test for correlation with alpha at .05. Figure 3.2 describes recruitment details.

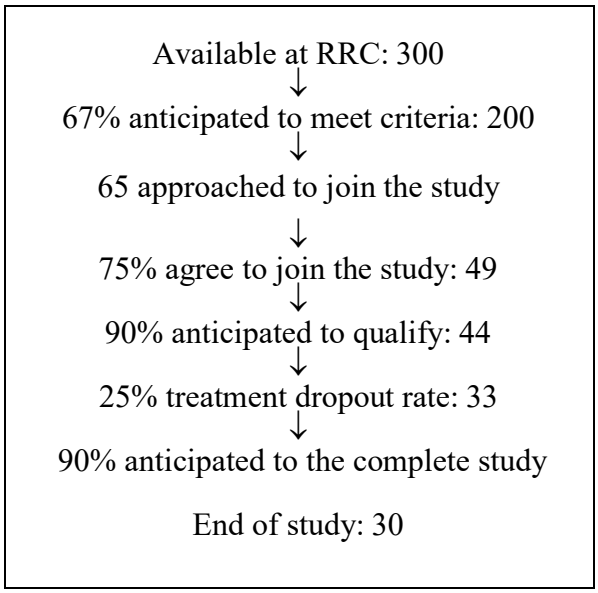


Figure 3.2. Participant Recruitment

Inclusion criteria for women receiving infertility treatment were: (1) age 20-44 years; (2) currently prescribed at least one oral daily dosed infertility medication under the care of a Reproductive Resource Center infertility provider; (3) ability to open an electronic monitoring cap with bottle as assessed by PI; (4) willingness to the use the electronic monitoring cap with bottle to store infertility medications; (5) self-administers infertility medication; (6) ability to read and write English; and (7) has a telephone or has access to a telephone. Women undergoing infertility diagnostic testing who have not begun taking infertility medications were excluded. Although ages of 15 to 44 years are considered female reproductive years, women younger than 20 years are not considered a population who seeks infertility services (Chandra et al., 2013). Women beyond the age of 44 are considered to have a significantly diminished reproductive potential (ASRM, 2012a).

A total targeted sample size of 30 participants were selected based on the power analysis and additional data generated from prior studies that assessed barriers of and

facilitators to MA in other patient populations using qualitative or mixed methods research designs (Castro, Santiago, Jiménez, Dávila-Vargas, Rosal, 2015; Claes, Decorte, Levtchenko, Knops, & Dobbels, 2014; Curioso, Kepka, Cabello, Segura, & Kurth, 2010; Ho, Jacob, & Tangiisuran, 2017). Unfortunately, similar studies are lacking in women undergoing infertility treatment. An adherence rate score of 1.00 was selected to divide the adherers from the non-adherers because no prior research has established infertility MA scores of less than 1.00 to achieve optimal reproductive outcomes. Moreover, infertility treatment practice guidelines have not documented adherence scores of less than 1.00 to be acceptable for establishing treatment effectiveness within the clinic setting (Gianaroli et al., 2012; Practice Committee of the American Society for Reproductive Medicine, 2006). More specifically, the effect of missed medication doses (dose-dependent efficacy) on pregnancy rates and surrogate measures of infertility treatment effectiveness (e.g., follicular development, changes in hormone levels, cervical mucus quality, and ovulation) has not been established.

Recruitment. During the clinic visit, infertility healthcare providers and nurses informed patients who met the inclusion criteria about the study and asked if they were willing to meet with the PI on the day of their visit. Infertility provider referral has been shown to be the most effective recruitment strategy during infertility research trials (Usadi et al., 2015). Prospective participants who agreed to meet with the PI were escorted to a private room located at the clinic where the PI greeted them and informed them further about the study. Those who opted to be enrolled in the study signed an IRB-approved consent form.

Minority recruitment. In comparison to United States population demographics, African American women and women of Hispanic ethnicity are underrepresented in the

population of women seeking infertility treatment services. This disparity has been attributed to a combination of economic, cultural, and social background factors (Daar et al., 2015; Green, Robins, Scheiber, Awadalla, & Thomas, 2001). White women represent 85.2% of clients seeking infertility treatment services, African-American women 10.2%, and other minorities 4.4% (Jain, 2006). In an effort to include minority women in this study, the infertility healthcare providers and nurses identified potential participants for recruitment. Also, the PI is an African-American female, which was assumed to enhance participant comfort level with study participation. Minority researchers possess unique insight from their own experiences and can anticipate important issues concerning cultural sensitivity matters (Vermund et al., 2018).

Setting

The participant population of interest, women receiving infertility treatment, were recruited from Reproductive Resource Center (RRC). Access was granted to the PI to conduct this study at RRC. A letter of support (see Appendix B) was provided by the owner, who is also the Medical Director. RRC is a reproductive endocrinology and infertility practice located in Overland Park, Kansas, which provides infertility services to women residing in urban, suburban, and rural regions of Kansas, Missouri, and neighboring states. This clinic serves approximately 300 women monthly (80% White, 10% Black/African American, 6% Hispanic/Latino, and 4% American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander) who could be screened for enrollment in this study. The racial/ethnic demographics of women seen at RRC are consistent with the general population of women who undergo infertility treatment at reproductive endocrinology and infertility centers nationally (Daar et al., 2015; Green et al., 2001; Jain, 2006). The ages of

women seen at RRC ranges from 20 to 49 years. RRC provides a full scope of infertility treatment including oral and injection medications, intrauterine insemination, and in-vitro fertilization. The RRC healthcare team includes two reproductive endocrinologists, six nurse practitioners, two registered nurses, and one medical assistant.

Conceptual Definitions

Background Factors. Background factors were conceptually defined as intrinsic and extrinsic factors that can influence women's beliefs about infertility medication-taking, such as age, race/ethnicity, education, and income.

Medication Adherence Barriers. Barriers to MA were conceptually defined as challenges and obstacles to adherence to infertility medication regimen.

Medication Adherence Facilitators. Facilitators of MA were conceptually defined as factors that promote adherence to infertility medication regimen.

Personal Experiences with Infertility Treatment. Personal experiences with infertility treatment were conceptually defined as women's thoughts and feelings regarding the personal impact of receiving infertility treatment.

Medication Adherence. MA was conceptually defined as the percent to which women's oral infertility medication-taking behaviors, with respect to taking, timing and dosing, are consistent with the infertility health care provider's prescription.

Instruments

Background Factors. Background factors were evaluated using a Demographic Questionnaire developed by the PI (see Appendix C) that assesses age, race/ethnicity, marital status, level of education, income, list of current infertility medications and dosing

schedules, and source of payment for infertility services (self-pay, partial out-of-pocket, fully insured).

Medication Adherence Barriers. MA barriers were measured using the ASK-20 Adherence Barrier Survey (Hahn et al., 2008) (see Appendix D). This 20-item self-administered survey takes approximately five minutes to complete. It addresses barriers to adherence based on knowledge, attitudes, social support, lifestyle, side effects, financial demands, relationship with healthcare provider, and overall medication taking. The ASK-20 Adherence Barrier Survey has a possible scoring range of 20 to 100. A five-point Likert type scale is used with a degree of agreement anchor response format of *Strongly Agree, Agree, Neutral, Disagree,* and *Strongly Disagree* for each item. Higher scores represent a greater number of barriers to MA. The ASK-20 Adherence Barrier Survey has a good internal consistency of .85 and a test-retest reliability of .80 (Hahn et al., 2008; Martza et al., 2008). Criterion validity was established with significant validity coefficient correlations of .20 to .61 between the ASK-20 Adherence Barrier Survey and several self-reported MA measures (Hahn et al., 2008; Martza et al., 2008). A letter of permission to use this survey is provided in the Appendix E.

Medication Adherence Facilitators. MA facilitators and personal experiences with infertility treatment were measured by the PI by conducting a structured interview using an Interview Guide (see Appendix F).

Personal Experiences of Infertility Treatment. Personal experiences with infertility treatment were measured by the PI by conducting a structured interview using an Interview Guide (see Appendix F).

Medication Adherence. MA was based on: (a) taking adherence—the percentage of prescribed doses taken, (b) dosing adherence—the percentage of days with correct dosing, and (c) timing adherence—the number of doses taken at 24 ± 6 hours (inter-dose intervals within 25% of the prescribed interval) for a once-daily regimen. MA was measured using the MEMS® (see Appendix G). A MEMS® diary was used to help validate the MEMS™ data (see Appendix H). MA data were retrieved from the MEMS® caps. The MEMS®8 Track CAP with liquid-crystal display (LCD) is a medication bottle cap containing microelectronics that record each cap removal and the time of the removal. Each MEMS® cap contains a battery and microelectronic circuitry that record a date and time with each cap removal from the bottle. The device has a 36-month battery life. Perfect accuracy on detection of time and date of cap removal has been observed with MEMS® usage (De Bleser et al., 2010). When the PI retrieved the caps from the participants, data were sent wirelessly to the password-protected medAmigo database, a platform that allows the PI to visualize participants' adherence data. A cumulative record of cap openings, beginning the day after the participant was instructed on use of the cap, was compiled for each participant. This report contained a listing and graphic of individual bottle openings and closings, the duration of opening, and the hours elapsed since the previous opening. Since accidental cap openings could occur, the MEMS® diary was used to document these events.

The MEMS® cap data were corrected by the PI using the MEMS® diary data. After any corrections were made, each cap removal was presumed to represent the patient ingesting one dose of the prescribed infertility medication. The MEMS® is considered accurate because it records the time and date of actual removal of the bottle cap (Denhaerynck et al., 2008). Limitations have been identified with the use of MEMS®,

including the inability to determine if the medication was consumed, failure to open the cap when the participant took out more than one dose of medication ahead of time to avoid carrying the MEMS® bottle around while away from home, and occurrences of bottle openings by mistake (Denhaerynck et al., 2008; Métry & Meyer, 1999; Russell et al., 2006). In effort to overcome such potential limitations, the PI reinforced the importance of documenting in the MEMS® diary if such incidences occurred. A summary of data collection approaches is provided in Table 3.1.

Table 3.1

Summary of Instruments

Variable	Measure	Psychometrics (reliability and validity)	Administration Time Points
Background Factors	Demographic Questionnaire	Not applicable	Baseline
Medication Adherence Barriers	ASK-20 Adherence Barrier Survey	Internal consistency reliability (Cronbach's alpha) = .85 Test-retest reliability =.80 Criterion validity = .20 to .61	Baseline
Medication Adherence Facilitators	PI conducting structured interviews	Not applicable	Baseline
Personal Experiences with Infertility Treatment	PI conducting structured interviews	Not applicable	Baseline
Medication Adherence	MEMS® and MEMS® diary	Microelectronic circuitry yields 100% accuracy detection on time and date of cap removal. 3-year battery life.	2 Months/2 Infertility Treatment Cycles

Procedure

The research protocol was approved by the Institutional Review Board (IRB) at the University of Missouri-Kansas City (UMKC). Dr. Celeste Brabec, Owner and Medical Director of RRC, deferred IRB review to UMKC (see Appendix I). The PI met with RRC clinic staff during a weekly staff meeting and provided study details and laminated inclusion/exclusion pocket cards for their convenience in identifying prospective participants. During the clinic visit, the infertility healthcare providers and nurses informed patients who meet the inclusion criteria about the study and asked if they were willing to meet with the PI on the day of their visit. Infertility provider referral has been shown to be the most effective recruitment strategy during infertility research trials (Usadi et al., 2015). However, the PI made the final determination of inclusion/exclusion for each individual referred to her. Prospective participants who agreed to meet with the PI were escorted to a private room located at the clinic, where the PI greeted and introduced herself to the participant and provided verbal explanation of the study's purpose, procedures, potential benefits and risks, possible scientific gains, and participation honoraria.

The PI reviewed the participants' rights and emphasized the voluntary nature of participation in the study. The potential participant was informed that participation in the study could be terminated at any point, and that participation or non-participation would have no influence on her care at RRC. The PI answered any questions that the individual had about the study. If the individual agreed to be in the study, the PI reviewed the consent and obtain informed consent. Individuals who declined to be enrolled in the full study would have been given an option to consent to provide their demographic information only (i.e., age, race/ethnicity, marital status, level of education, income, and source of payment for

infertility services (self-pay, partial out-of-pocket, fully insured). This would have allowed the PI to assess and compare the demographics of those who consented to be enrolled in the study and those who declined to be enrolled in the study.

The PI collected the telephone numbers of participants. If the consented participant was not able to complete baseline visit activities on the day of this clinic visit, the PI offered the participant the option of completing these activities during a scheduled visit at a location of choice or at the next scheduled clinic visit. If the participant preferred a visit at a location of choice, the PI scheduled that visit and obtained the location address in addition to the telephone number that was collected. If the participant opted to complete the initial study activities at the next clinic appointment, the PI obtained the appointment date and time from the participant and confirmed this appointment with a member of the front office clinic staff. On clinic days when the PI was not present, yet infertility providers identified patients who met study criteria and expressed interest in being enrolled in the study, the providers and nurses maintained these names and telephone numbers for the PI. The PI later called these women and offered them the option of a scheduled visit at a location of choice or seeing them at their next scheduled clinic visit, where informed consent was obtained.

The PI demonstrated skills for establishing and maintaining rapport with participants throughout the study. The baseline visit (see Steps 1 to 4, below) lasted approximately 35 to 40 minutes. The remaining one to two months of the study consisted of infertility medication-taking monitoring with MEMS®, MEMS® diary, and one to two follow-up telephone calls (see Step 5). Study activities are described below:

- Step 1: (Total time 5 minutes). The PI administered a Demographic Questionnaire.

- Step 2: (Total time 5 minutes). The PI administered the ASK-20 Adherence Barrier Survey.
- Step 3: (Total time 10 to 15 minutes). The PI conducted the structured interview.
- Step 4: (Total time 15 minutes). The PI trained the participant on how to use the MEMS® and MEMS® diary for the two-month electronic monitoring phase. The participant used the MEMS® cap with one randomly selected infertility medication that was to be taken once daily. Only one prescribed infertility medication was monitored because prior research has shown that monitoring a second medication does not provide additional MA information (Haynes et al., 2006). When applicable, the PI numbered all the once-daily administered infertility medications listed on the Demographics Questionnaire. The PI entered that number into a random numbers generator and had the participant monitor the infertility medication that was randomly selected. The PI instructed the participant to (1) place one of the infertility medications into the MEMS®, bottle, (2) keep the medication in the bottle and not take it from any other containers, and (3) place all new refills of the medication into the bottle. The participant was instructed on the use of the MEMS® diary to document any accidental cap openings, openings when no medication was ingested (e.g., when refilling MEMS® bottle), and early openings when a medication was removed early to take later, but on time. The participant was given specific examples of when the diary should and should not be used. The participant was then trained to store the diary with the MEMS® bottle. Training continued until the participant achieved 100% accuracy using the MEMS® diary with the four

MEMS® diary test scenarios (accidental opening, early opening, opened but no medication administered, diary storage). The PI gave the participant an addressed envelope with prepaid postage to mail the MEMS® cap device to the PI at study completion. A $25.00 gift card was given to the participant as an honorarium.

- Step 5: (Total time: one to two months). The PI assessed infertility medication taking behaviors during one to two months of electronic monitoring. This two-month timeframe was selected to avoid the Hawthorne effect, because a monitoring period under one month has been shown in prior studies to be less reliable (De Bleser et al., 2011). However, in the current study, the first month of MEMS® data was not discarded because infertility treatment often requires intervals of stopping and restarting medications cyclically; thus the likelihood of the Hawthorne effect would not be weakened over time. The participant used the MEMS® and MEMS® diary as described in Step 4 for a duration of one to two treatment cycles. If the participant became pregnant prior to study completion, the participant was instructed to notify the PI and to discontinue the MEMS® and MEMS® diary and mail them to the PI as described below. The PI conducted one-month and two-month follow-up telephone calls (lasting approximately five minutes, see Appendix J) to make sure the participant was using the MEMS® correctly after the training and to assess if there were any questions or concerns about the MEMS® diary. After one to two months, the participant mailed the MEMS® diary and MEMS® cap device to the PI so that she could retrieve data through the MEMS® software program. Upon receiving

the MEMS™ cap device and diary, the PI mailed the participant a second $25.00 gift card as an honorarium.

Risk Reduction

IRB approval (Protocol Number: 18-262) was obtained from UMKC. Dr. Celeste Brabec, Owner and Medical Director of RRC, deferred IRB review to UMKC (see Appendix I). Once the study was initiated, participants' confidentiality was maintained using the following techniques: (1) the PI was responsible for all data management, (2) each participant was given a unique study identification code to enable data source merging (e.g., demographics, MEMS® data), (3) the unique study identification codes were stored in a locked separate file, (4) all data were entered and stored in the password-protected REDCap data system, (5) all participant names and other identifiers were removed from the data upon assignment of a study identification code.

The risk of physical harm was minimal for participants in this protocol. The study procedures were designed to not interfere with routine medical care; thus there was little potential for adverse events directly related to study procedures. The study procedures were performed parallel to the infertility treatment care plan; therefore, study participation did not introduce direct medical or physical risk to the patient. To further reduce possible physical risk, the PI was trained regarding situations when she should refer the participant to the infertility clinic, forward information to the infertility clinic, or contact the infertility care team directly. The PI is also a DNP-prepared infertility nurse practitioner. The PI was aware that the data collection process could generate emotional responses during the interviews. If this had occurred, the PI would have provided the participant time to express significant emotion, acknowledge the importance of this to the wellbeing of the participant, and refer

her to a licensed counselor who specializes in struggles associated with infertility (Complementary Care Group, 2012).

Adverse events related to using MEMS® were unlikely. However, the PI asked participants during each telephone encounter if they experienced any MEMS®-related problems with taking their medications. Any perceived problems would have been documented exactly as participants presented them. The PI would have probed with follow-up questions. Any significant events would have been shared immediately with the infertility practice clinic manager. Any participant who appeared to have experienced an adverse event related to using the MEMS® would have been immediately withdrawn from the study and IRB would have been notified.

Data Management

All study data were maintained in the password-protected Research Electronic Data Capture ([REDCap], 2006) data system. The electronic medication monitoring data, identified only by the participant's unique code number, was encrypted and sent wirelessly to the MEMS® database. Only aggregate data were reported. Data analysis was conducted by the PI using SPSS version 24 (IBM Knowledge Center, n.d.) and supervised by Dr. A. Cheng, the University of Missouri-Kansas City biostatistician. The PI took all measures to ensure all data points were collected; however if missing data were more than 10% in this study, multiple imputation technique would have been employed to guarantee the best statistical analysis results.

Data Analysis

For demographic data, percentages, means, ranges, and standard deviations are reported.

Hypothesis 1. Women with a greater number of perceived barriers will demonstrate lower infertility MA scores than women with a lesser number of perceived barriers.

Analysis plan. The assumption of normality was not met for the distribution of MA scores based on the small sample size (n=18) that used MEMS®. Thus Spearman's rho correlation coefficient was computed to assess the relationship between perceived barriers measured with the ASK-20 Adherence Barrier Survey (independent variable) and MA scores (dependent variable) measured with one to two months of MEMS® data at a significance level of .05.

Hypothesis 2. Women with a greater number of perceived facilitators will demonstrate higher MA scores than women with a lesser number of perceived facilitators.

Analysis plan. The interviews were audiotaped, transcribed, and data coded using a thematic approach. Response codes with functionally equivalent meaning were assigned to thematic categories. Those with overlapping themes were merged into one category. Thematic categories were transformed into quantitative counts (encoded to thematic variables). The assumption of normality was not met for the distribution of MA scores based on the small sample size (n=18) that used MEMS®. The Spearman's rho correlation coefficient was computed to assess the relationship between the number of thematic (independent) variables, representing perceived facilitators, and measured MA scores (dependent variable) measured with one to two months of MEMS® data at a significance level of .05.

Hypothesis 3. Differences will exist among perceived barriers and facilitators between women who were adherent and women who were non-adherent.

Analysis plan. The assumption of normality was not met for the distribution of MA scores based on the small sample size (n=18) that used MEMS®. The Mann-Whitney U test or the Chi-Square test was used to compare group differences in perceived barriers measured by the ASK-20 Adherence Barrier Survey and thematic perceived facilitator variables between two groups—women who were adherent and women who were non-adherent—at a significance level of .05. Degree of adherence was dichotomized as the following: adherent group=MEMS® adherence score of 100% and non-adherent group=MEMS® adherence score of less than 100%.

Hypothesis 4. Differences will exist in women's personal experiences with infertility treatment based on women's age, race/ethnicity, level of education, income, and infertility insurance status.

Analysis plan. The interviews were audiotaped, transcribed, and data coded using a thematic approach. Response codes with functionally equivalent meaning were assigned to thematic categories. Those with overlapping themes were merged into one category. The Chi-Square Test was used to determine if there were statistically significant differences between quantified thematic categories (personal experiences) and five categorical (nominal) variables (age, race/ethnicity, level of education, income, and insurance status) at a significance level of .05.

Hypothesis 5. Differences will exist between adherent and non-adherent women by age, race/ethnicity, level of education, income, and infertility insurance status.

Analysis plan. Level of adherence was dichotomized as the following: adherent group=MEMS® adherence score of 100% and non-adherent group=MEMS® adherence score of less than 100%. The assumption of normality was not met for the distribution of

MA scores based on the small sample size. (n=18) that used MEMS®. The Chi-Square test was used to determine if there were statistically significant differences between the two dichotomized variables (adherent versus non-adherent) and five categorical (nominal) variables (age, race/ethnicity, level of education, income, and insurance status) at a significance level of .05.

Exploratory hypothesis. Differences will exist between women who were adherent and women who were non-adherent based on women's personal experiences with undergoing infertility treatment.

Analysis plan. Level of adherence was dichotomized as the following: adherent group=MEMS® adherence score of 100% and non-adherent group=MEMS® adherence score of less than 100%. The assumption of normality was not met for the distribution of MA scores based on the small sample size. The Chi-Square test was used to determine if there were statistically significant differences between the two dichotomized variables (adherent versus non-adherent) and categorical (nominal) thematic personal experiences with undergoing infertility treatment at a significance level of .05.

CHAPTER 4

RESULTS

Chapter 4 is a report of findings related to the research questions. This chapter is organized by recruitment and enrollment, participant characteristics, the primary research question and working hypotheses, the secondary research question and secondary hypotheses, and the exploratory research question and exploratory hypothesis.

Recruitment and Enrollment

Participants were recruited from October 2018 to December 2018 from Reproductive Resource Center. Forty-seven participants were invited to take part in the study but 17 declined this invitation, which yielded 30 participants enrolled in the study and a 64% consent rate. Demographic data were not obtained on those who declined participation because consent to obtain demographic data would have occurred when the PI spoke with these individuals. However, these 17 individuals informed the infertility clinic providers that they did not want the PI to contact them. Reasons they declined to take part in the study and declined PI contact were not obtained.

All 30 consented participants completed the demographics questionnaire, MA barriers questionnaire, and the structured interviews. Forty percent (n=12) of the women did not use MEMS® because four became pregnant, four decided to pursue IVF, three decided to discontinue infertility treatment, and one decided to pursue embryo donation. Of the 18 (60%) participants who used MEMS® during infertility treatment cycles, 33.3% (n=6) used MEMS® for two treatment cycles. Sixty-seven percent (n=12) of the women used MEMS® for one treatment cycle because three decided to pursue IVF, three decided to suspend treatment indefinitely, three did not follow MEMS® protocol and returned the MEMS®

caps prior to the second treatment cycle, one decided to discontinue infertility treatment, one became pregnant, and one had provider-deferred treatment plan secondary to experiencing menstrual problems. Figure 4.1. depicts a flow diagram using STROBE Statement Guidelines.

Patient Characteristics

The mean age of all participants was 31.3 (SD= 3.93) years with a range of 24 to 39. Baseline sample demographic data (background factors) are found in Tables 4.1 and 4.2. Participants were predominately White 83.3% (25/30), Non-Hispanic 90% (27/30), married 100% (30/30), aged 25 to 30 years 43.3% (13/30), resided in a suburban community 83.3% (25/30), had a $75,000 to $99,999 household income 30% (9/30), held a Bachelor's degree 50% (15/30), had partial out-of-pocket payment responsibility for infertility treatment services 56.7% (17/30), had no prior child 80% (24/30), and experienced two to three prior unsuccessful treatment cycles 46.7% (14/30).

The mean age of the 18 (60%) participants who used the MEMS® was 31.8 (SD= 3.65) years with a range of 24 to 39. Baseline sample demographic data (background factors) are found in Tables 4.1 and 4.2. Participants were predominantly White 83.3% (15/18), Non-Hispanic 94.4% (17/18), married 100% (18/18), aged 31 to 35 years 44.7% (8/18), resided in a suburban community 88.9% (16/18), had a $75,000 to $99,999 household income 27.8% (5/18), held a Bachelor's degree 61.1% (11/18), had partial out-of-pocket payment responsibility for infertility treatment services 50% (9/18), had no prior child 76.8% (14/18), and either experienced zero to one 38.9% (7/18) or two to three prior unsuccessful treatment cycles 38.9% (7/18).

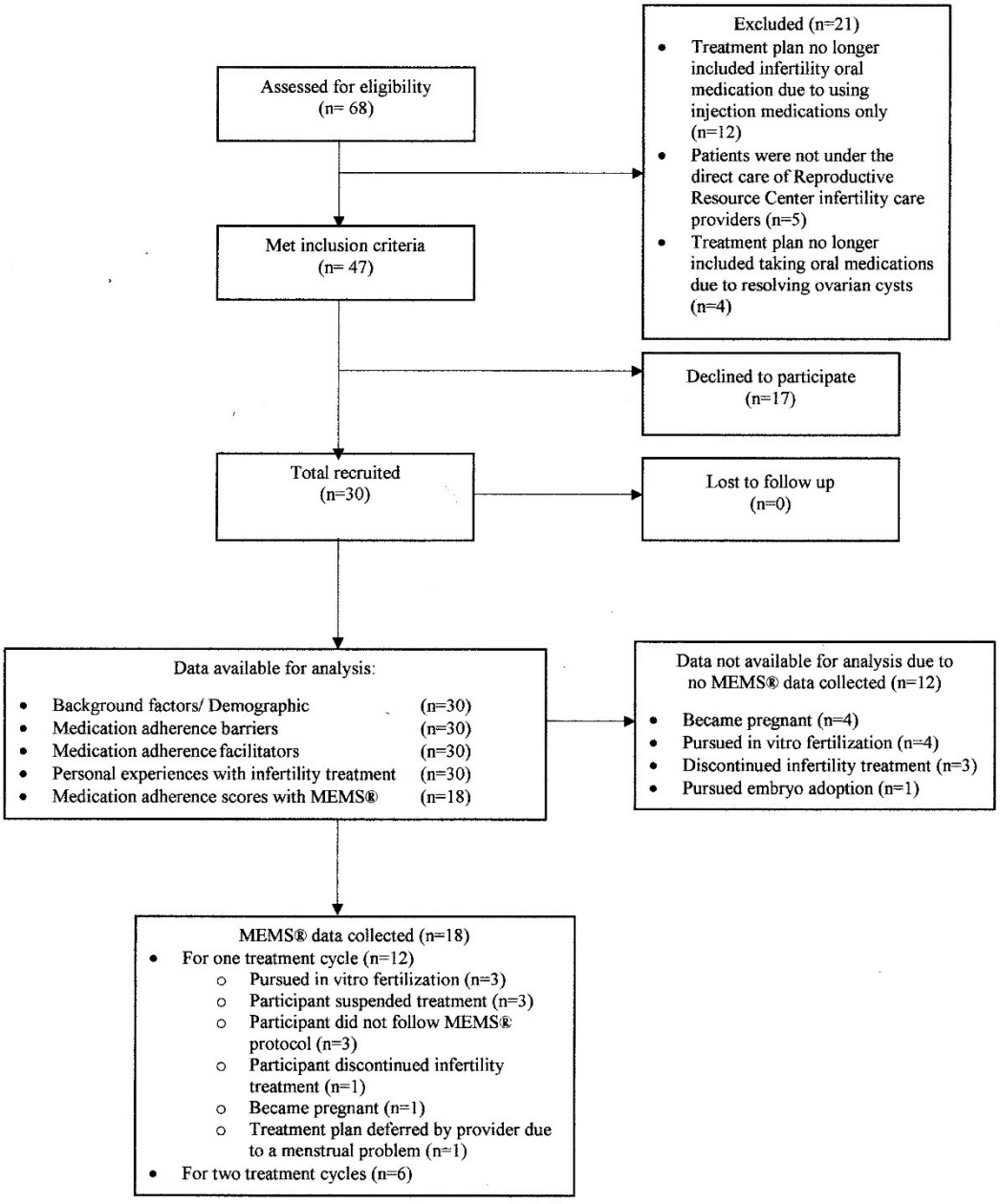


Figure 4.1. Flow Diagram using STROBE Statement Guidelines
MEMS®= Medication Event Monitoring System®

Table 4.1

Sample Demographics

Background Factors	Total Sample n (%)	Participants who used MEMS® n (%)
Race		
Non-Hispanic White	25 (83.3)	15 (83.3)
Hispanic or Mexican American	2 (6.7)	1 (5.6)
Asian	1 (3.3)	1 (5.6)
Black or African-American	1 (3.3)	1 (5.6)
American Indian or Alaskan Native	1 (3.3)	0
Ethnicity		
Non-Hispanic or Latino	27 (90)	17 (94.4)
Hispanic or Latino	3 (10)	1 (5.6)
Marital Status		
Married	30 (100)	18 (100)
Age Range		
20-24 years	1 (3.3)	1 (5.6)
25-30 years	13 (43.3)	7 (38.9)
31-35 years	12 (40)	8 (44.4)
36-40 years	4 (13.3)	2 (11.1)
Residence		
Suburban	25 (83.3)	16 (88.9)
Rural	3 (10)	1 (5.6)
Urban	2 (6.7)	1 (5.3)

Note. MEMS® = Medication Event Monitoring System. Total n=30.
Participants who used MEMS® n= 18

Table 4.2

Sample Demographics

Background Factors	Total Sample n (%)	Participants who used MEMS® n (%)
Household Income		
$50,000-$74,999	4 (13.3)	3 (16.7)
$75,000-$99,999	9 (30)	5 (27.8)
$100,000-$124,000	7 (23.3)	4 (22.2)
$125,000-$149,999	5 (16.7)	3 (16.7)
More than $150,000	5 (16.7)	3 (16.7)
Highest Level of Education		
High School Graduate, Diploma, or Equivalent	2 (6.7)	1 (5.6)
Some College, No Degree	2 (6.7)	1 (5.6)
Associate Degree	5 (16.7)	3 (16.7)
Bachelor's Degree	15 (50)	11 (61.1)
Master's Degree	5 (16.7)	2 (11.1)
Doctorate Degree	1 (3.3)	0
Level of Infertility Insurance Coverage		
Partial Out-of-Pocket	17 (56.7)	9 (50)
All Self-Pay	12 (40)	8 (44.4)
Full Coverage	1 (3.3)	1 (5.6)
Has At Least One Child		
No	24 (80)	14 (77.8)
Yes	6 (20)	4 (22.2)
Number of Prior Treatment Cycles at Current Clinic		
0-1	11 (36.7)	7 (38.9)
2-3	14 (46.7)	7 (38.9)
4 or greater	5 (16.7)	4 (22.2)

Note. MEMS® = Medication Event Monitoring System. Total n=30. Participants who used MEMS® n= 18

Primary Research Question

What do women undergoing infertility treatment perceive as barriers to and facilitators of MA that influence their medication-taking behaviors?

Hypothesis 1

Women with higher MA barrier scores will demonstrate lower infertility MA scores than women with lower MA barrier scores.

Medication adherence scores. A total of 18 (60%) of the 30 participants used MEMS® with infertility medication-taking for either one or two treatment cycles and 12 (40%) participants did not use MEMS®. Reasons why participants either did not use MEMS® (n=12) or used MEMS® for only one treatment cycle (n=12) are described in the Flow Diagram in Figure 4.1. Of the 18 (60%) participants who used the MEMS®, 12 (66.7%) women used MEMS® for one treatment cycle, and six (33.3%) women used MEMS® for two treatment cycles.

The median adherence MA score all 18 participants who used MEMS® score was 0.975 (SD .078) with a range of 0.75 to 1.00. The median adherence rate of women who used MEMS® for two treatment cycles (n= 6) was .0975 (SD .060), and the median adherence score of women who used MEMS® for one treatment cycle (n= 12) was 0.95 (SD .087). There was no not significant difference (p= 0.616) in the median adherence scores between those who used MEMS® for one versus two treatment cycles.

Medication adherence barrier scores. The barrier scores of ASK-20 Adherence Barrier Survey had a possible range of 20 to 100, with higher scores representing greater barriers to adherence. The mean total barrier score was 34.5 (SD 7.04) with a range of 25 to 49 for all 30 participants. Of the 18 (60%) participants who used MEMS®, the median total barrier score was 34 (SD 7.18) with a range of 25 to 49. Of the 12 (40%) participants who did not use MEMS®, the median total barrier score was 35.5 (SD 6.96) with a range of 25 to 42. There was no significant difference (p= 0.433) in the median total barriers scores

between those who used MEMS® and those who did not. The most commonly reported barriers to medication-taking of the total sample (n=30) included recently feeling sad, down, or blue (53%, n=16), taking medication more than once per day (40%, n=12), forgetting things that were important (20%, n=6), worrying if the medication would affect sexual health (17%, n=5), and forgetting to take medication (10%, n=3). Regarding past medication-taking behaviors within the last week to three months, women reported taking medication more or less than prescribed (20%, n=6), not having the medication with them when it was time to take it (16.7%, n=5), and having skipped or stopped taking a medication because it made them feel bad (3.3%, n=1). Participant response percentages to the ASK-20 Adherence Barrier Survey items are listed in Tables 4.3 and 4.4. Statistical significance was set at $p < 0.05$. There was a significant negative correlation ($r = -.49$; $p=.020$) between the total median barrier scores and MA the scores.

Hypothesis 2

Women with a greater number of perceived facilitators will demonstrate higher MA scores than women with a lesser number of perceived facilitators.

Medication adherence scores and facilitators. The mean number of facilitators reported per participant was 3 (SD 1.41) with a range of 1 to 6 for all 30 participants. Of the 18 (60%) participants who used MEMS®, the median number of facilitators reported per participant was 3 (SD 1.30) with a range of 1 to 6. Of the 12 (40%) participants who did not use MEMS®, the median number of facilitators reported was 2.5 (SD 1.60) with a range of 1 to 6. There was no significant differences ($p= 0.339$) in the median number of reported facilitators between those who used MEMS® and those who did not. Emerging themes of

Table 4.3

Responses to the ASK-20 Adherence Barrier Survey Concerning Medication Adherence Barriers by All Participants

	% (n) Strongly Agree	% (n) Agree	% (n) Neutral	% (n) Disagree	% (n) Strongly Disagree
I just forget to take my medicine some of the time.	3.3 (1)	6.7 (2)	3.3 (1)	13.3 (4)	73.3 (22)
I run out of my medicine because I don't get refills on time.	0	3.3(1)	3.3(1)	20 (6)	73.3 (22)
My use of alcohol gets in the way of taking my medicines.	0	0	0	13.3(4)	86.7(26)
I worry about how medicine will affect my sexual health.	0	16.7 (5)	13.3 (4)	13.3 (4)	56.7 (17)
I sometimes forget things that are important to me.	0	20 (6)	3.3 (1)	36.7 (11)	40 (12)
I have felt sad, down, or blue during the past month.	13.3 (4)	40 (12)	10 (3)	26.7 (8)	10 (3)
I feel confident that each one of my medicines will help me.	26.7 (8)	53.3 (16)	16.7 (5)	3.3 (1)	0
I know if I am reaching my health goals.	13.3 (4)	66.7 (20)	16.7 (5)	3.3 (1)	0
I have someone I can call with questions about my medicines.	46.7 (14)	46.7 (14)	3.3 (1)	0	3.3 (1)
I understand my doctor's/nurse's instructions about the medicines I take.	60 (18)	40 (12)	0	0	0
My doctor/nurse and I work together to make decisions.	46.7 (14)	40 (12)	13.3 (4)	0	0
I am able to read and understand pill bottle labels.	73.3 (22)	23.3 (7)	3.3 (1)	0	0
Taking medicines more than once a day is inconvenient.	6.7 (2)	33.3 (10)	13.3 (4)	26.7 (8)	20 (6)
I have to take too many medicines a day.	0	20 (6)	13.3 (4)	26.7 (8)	40 (12)
It is hard for me to swallow the pills I have to take.	0	6.7 (2)	0	23.3 (7)	70 (21)

Note. n=30

Table 4.4

Responses to the ASK-20 Adherence Barrier Survey Concerning Medication-taking Behaviors by All Participants

	% (n) In the last week	% (n) In the last month	% (n) In the last 3 months	% (n) More than 3 months ago	% (n) Never
Have you taken medicine more or less than prescribed?	10 (3)	3.3 (1)	6.7 (2)	6.7 (2)	73.3 (22)
Have you skipped or stopped taking a medicine because you didn't think it was working?	0	0	0	10 (3)	90 (27)
Have you skipped or stopped taking a medicine because it made you feel bad?	0	0	3.3 (1)	16.7 (5)	80 (24)
Have you skipped, stopped, not refilled, or taken less medicine because of cost?	0	0	0	6.7 (2)	93.3 (28)
Have you not had medicine with you when it was time to take it?	0	10 (3)	6.7 (2)	30 (10)	53.3 (15)

Note. n=30

MA facilitators were categorized as (a) routine related, (b) physical aid related, (c) healthcare provider related, (d) knowledge related, (e) attitudes and beliefs related, (f) cognition related, (g) motivation related (h), control beliefs related, and (i) social support related. Routine related facilitators included associating pill-taking with a specific mealtime or taking pills after brushing teeth. Physical aid facilitators included activities such as placing pills in a location easily visible or using a mobile phone alarm as a reminder. Health provider related facilitators included receiving health provider instructions and feeling health provider optimism concerning treatment plan. Knowledge related facilitators included understanding about how the medicine works. Attitudes and beliefs related facilitators included thinking and hoping the medication will work. Cognition related facilitators included ability to remember to take medication.

Motivation related facilitators included feeling a personal drive to take the medication. Control beliefs related facilitators included having a mental sense of control over circumstances. Social support related facilitators included partner reminders and having the support of important others. A detailed list of facilitators with participant response percentages is provided in Table 4.5. The most commonly reported facilitators categories were physical aid related (60%, n=18), routine related (50%, n=15), social support related (43%, n=13), and motivation related (27%, n=8). Statistical significance is set at $p < 05$. The correlation between the number of facilitators reported per participant and MA scores was not significant ($r = -.02$; $p= 0.462$).

Hypothesis 3.

Differences will exist among perceived barriers and facilitators between women who are adherent and non-adherent to their infertility medication regimen.

Table 4.5

Medication Adherence Facilitator Thematic Categories Based on Data from All Participants

Facilitator Type	% Within Facilitator Category	% Total Sample (n=30)
Physical Related (n= 18)		60
Using a mobile phone alarm (n=10)	55.5	
Placing pills at a location easily visible (n=9)	50	
Placing pills in medicine cabinet or pill box (n=6)	33.3	
Using a written schedule (e.g. personal diary) (n=2)	11.1	
Keeping pills in possession (e.g. purse) (n=1)	5.5	
Routine Related (n=15)		50
Taking pills at mealtime or bedtime (n=11)	73.3	
Taking pills during a routine activity (e.g. brushing teeth) (n=2)	13.3	
Taking pills with other routine medications (e.g. prenatal vitamins) (n=4)	26.7	
Social Support Related (n=13)		43.3
Partner reminders (n=10)	76.9	
Feeling support from important others (n=5)	38.4	
Hearing about the treatment success stories of other women (n=2)	15.4	
Motivation Related (n=8)		26.7
Possessing sense of personal drive/motivation (n=8)	100	
Attitudes and Beliefs Related (n=6)		20
Thinking the medication will work (n=3)	50	
Hoping the medication will work (n=3)	50	
Heath Care Provider Related (n=5)		16.7
Health care provider instructions (n=4)	80	
Health care provider optimism (n=1)	20	

Table continues

Facilitator Type	% Within Facilitator Category	% Total Sample (n=30)
Cognition Related (n=3)		10
Ability to remember to take pills (n=3)	100	
Control Belief Related (n=2)		6.7
Possessing sense of control over circumstances (n=2)	100	
Knowledge Related (n=1)		3.3
Understanding how the medication works (n=1)	100	

Note. Total sample size = 30. Sample size varies within facilitator categories.

Degree of adherence was dichotomized as follows: adherent group= MEMS® adherence score of 100% and non-adherent group= MEMS® adherence score of less than 1.00. Of the 18 participants (60%) who used MEMS®, nine (50%) participants had an adherence rate of 1.00. The remaining nine participants (50%) had adherence scores ranging from 0.75 to 0.95 with a median rate of 0.90. Statistical significance is set at $p < 0.05$. Women in the non-adherent group had a significantly ($p= 0.019$) higher median total barrier score of 39.0 (SD= 6.49) compared to women in the adherent group with an median total barrier score of 30.0 (SD= 5.79). Tables 4.6 and 4.7 present ASK-20 Adherence Barrier Survey item response percentages based on women who were adherent to their infertility medication regimen. Tables 4.8 and 4.9 present ASK-20 Adherence Barrier Survey item response percentages based on women who were non-adherent to their infertility medication regimen.

No significant difference was observed with the number of perceived facilitators reported between women who were adherent and women who were non-adherent. The group who were adherent had a median of 3.00 (SD 1.20) facilitators with a range of 2 to 5 facilitators, and the group who were non-adherent had a median of 3.00 (SD 1.45) facilitators with a range of 1 to 6 facilitators. There were no significant differences found in types of facilitators reported between the two groups of women. Table 4.10 presents facilitators and participant response percentages based on women who were adherent to their infertility medication regimen. Table 4.11 presents facilitators and participant response percentages based on women who were non-adherent to their infertility medication regimen.

Table 4.6

Responses to the ASK-20 Adherence Barrier Survey Concerning Medication Adherence Barriers by Participants Who Were Adherent

	% (n) Strongly Agree	% (n) Agree	% (n) Neutral	% (n) Disagree	% (n) Strongly Disagree
I just forget to take my medicine some of the time.	0	0	0	0	100(9)
I run out of my medicine because I don't get refills on time.	0	0	11.1 (1)	11.1 (1)	77.8 (7)
My use of alcohol gets in the way of taking my medicines.	0	0	0	0	100 (9)
I worry about how medicine will affect my sexual health.	0	11.1 (1)	11.1 (1)	11.1 (1)	66.7 (6)
I sometimes forget things that are important to me.	0	11.1 (1)	0	33.3 (3)	55.6 (5)
I have felt sad, down, or blue during the past month.	11.1 (1)	22.2 (2)	11.1 (1)	33.3 (3)	22.2 (2)
I feel confident that each one of my medicines will help me.	33.3 (3)	66.7 (6)	0	0	0
I know if I am reaching my health goals.	22.2 (2)	33.3 (3)	44.4 (4)	0	0
I have someone I can call with questions about my medicines.	44.4 (4)	55.6 (5)	0	0	0
I understand my doctor's/nurse's instructions about the medicines I take.	55.6 (5)	44.4 (4)	0	0	0
My doctor/nurse and I work together to make decisions.	44.4 (4)	55.6 (5)	0	0	0
I am able to read and understand pill bottle labels.	77.8 (7)	22.2 (2)	0	0	0
Taking medicines more than once a day is inconvenient.	0	11.1 (1)	33.3 (3)	33.3 (3)	22.2 (2)
I have to take too many medicines a day.	0	22.2 (2)	0	22.2 (2)	55.6 (5)
It is hard for me to swallow the pills I have to take.	0	11.1 (1)	0	22.2 (2)	66.7 (6)

Note. n=9

Table 4.7

Responses to the ASK-20 Adherence Barrier Survey Concerning Medication-taking Behaviors by Participants Who Were Adherent

	% (n) In the last week	% (n) In the last month	% (n) In the last 3 months	% (n) More than 3 months ago	%(n) Never
Have you taken medicine more or less than prescribed?	22.2 (2)	0	0	0	77.8(7)
Have you skipped or stopped taking a medicine because you didn't think it was working?	0	0	0	0	100 (9)
Have you skipped or stopped taking a medicine because it made you feel bad?	0	0	0	22.2 (2)	77.8 (7)
Have you skipped, stopped, not refilled, or taken less medicine because of cost?	0	0	0	0	100 (9)
Have you not had medicine with you when it was time to take it?	0	0	11.1 (1)	22.2 (2)	66.7 (6)

Note. n=9

Table 4.8

Responses to the ASK-20 Adherence Barrier Survey Concerning Medication Adherence Barriers by Participants Who Were Non-adherent

	% (n) Strongly Agree	% (n) Agree	% (n) Neutral	% (n) Disagree	% (n) Strongly Disagree
I just forget to take my medicine some of the time.	0	11.1 (1)	11.1 (1)	11.1 (1)	66.7 (6)
I run out of my medicine because I don't get refills on time.	0	0	0	44.4 (4)	55.6 (5)
My use of alcohol gets in the way of taking my medicines.	0	0	0	33.3(3)	66.7(6)
I worry about how medicine will affect my sexual health.	0	22.2 (2)	22.2 (2)	22.2 (2)	33.3 (3)
I sometimes forget things that are important to me.	0	22.2 (2)	0	44.4 (4)	33.3 (3)
I have felt sad, down, or blue during the past month.	0	55.6 (5)	0	33.3 (3)	11.1 (1)
I feel confident that each one of my medicines will help me.	11.1 (1)	44.4 (4)	44.4 (4)	0	0
I know if I am reaching my health goals.	0	88.9 (8)	11.1 (1)	0	0
I have someone I can call with questions about my medicines.	22.2 (2)	55.6 (5)	11.1 (1)	0	11.1 (1)
I understand my doctor's/nurse's instructions about the medicines I take.	33.3 (3)	66.7 (6)	0	0	0
My doctor/nurse and I work together to make decisions.	11.1 (1)	66.7 (6)	22.2 (2)	0	0
I am able to read and understand pill bottle labels.	55.6 (5)	33.3 (3)	11.1 (1)	0	0
Taking medicines more than once a day is inconvenient.	11.1 (1)	44.4 (4)	11.1 (1)	33.3 (3)	0
I have to take too many medicines a day.	0	33.3 (3)	11.1 (1)	44.4 (4)	11.1 (1)
It is hard for me to swallow the pills I have to take.	0	11.1 (1)	0	44.4 (4)	44.4 (4)

Note. n=9

Table 4.9

Responses to the ASK-20 Adherence Barrier Survey Concerning Medication-taking Behaviors by Participants Who Were Non-adherent

	% (n) In the last week	% (n) In the last month	% (n) In the last 3 months	% (n) More than 3 months ago	% (n) Never
Have you taken medicine more or less than prescribed?	0	0	11.1 (1)	11.1 (1)	77.8 (7)
Have you skipped or stopped taking a medicine because you didn't think it was working?	0	0	0	22.2(2)	77.8 (7)
Have you skipped or stopped taking a medicine because it made you feel bad?	0	0	11.1 (1)	33.3 (3)	55.6 (5)
Have you skipped, stopped, not refilled, or taken less medicine because of cost?	0	0	0	22.2 (2)	77.8 (7)
Have you not had medicine with you when it was time to take it?	0	11.1 (1)	11.1 (1)	55.6 (5)	22.2 (2)

Note. n=9

Table 4.10

Medication Adherence Facilitator Thematic Categories Based on Data from Participants Who Were Adherent

Facilitator Type	% Within Facilitator Category	% Total Sample (n=9)
Physical Related (n=6)		66.6
Placing pills at a location easily visible (n=1)	16.7	
Placing pills in medicine cabinet or pill box (n=1)	16.7	
Keeping pills in possession (e.g. purse) (n=0)	0	
Using a mobile phone alarm (n=5)	83.3	
Using a written schedule (e.g. personal diary) (n=2)	33.3	
Social Support Related (n=6)		66.6
Partner reminders (n=5)	83.3	
Feeling support from important others (n=0)	0	
Hearing about the treatment success stories of other women (n=1)	16.7	
Attitudes and Beliefs Related (n=4)		44.4
Thinking the medication will work (n=2)	50	
Hoping the medication will work (n=2)	50	
Routine Related (n=4)		44.4
Taking pills at mealtime or bedtime (n=3)	75	
Taking pills during a routine activity (e.g. brushing teeth) (n=1)	25	
Taking pills with other routine medications (e.g. prenatal vitamins) (n=0)	0	
Motivation Related (n=3)		33.3
Possessing sense of personal drive/motivation (n=3)	100	
Heath Care Provider Related (n=2)		22.2
Health care provider instructions (n=2)	100	
Health care provider optimism (n=0)	0	
Being involved in plan of care (n=0)	0	

Table continues

Facilitator Type	% Within Facilitator Category	% Total Sample (n=9)
Control Belief Related (n=1)		11.1
Possessing sense of control over circumstances	100	
Knowledge Related (n=0)		0
Understanding how the medication works (n=0)	0	
Cognition Related (n=0)		0
Ability to remember to take pills (n=0)	0	

Note. Total sample size = 9. Sample size varies within facilitator categories.

Table 4.11

Medication Adherence Facilitator Thematic Categories Based on Data from Participants Who Were Non-adherent

Facilitator Type	% Within Facilitator Category	% Total Sample (n=9)
Routine Related (n=7)		77.8
Taking pills at mealtime or bedtime (n=6)	85.8	
Taking pills during a routine activity (e.g. brushing teeth) (n=1)	14.3	
Taking pills with other routine medications (e.g. prenatal vitamins) (n=2)	28.6	
Social Support Related (n=5)		55.6
Partner reminders (n=2)	40	
Feeling support from important others (n=3)	60	
Hearing about the treatment success stories of other women (n=1)	20	
Physical Related (n=4)		44.4
Placing pills at a location easily visible (n=2)	50	
Placing pills in medicine cabinet or pill box (n=1)	25	
Keeping pills in possession (e.g. purse) (n=0)	0	
Using a mobile phone alarm (n=1)	25	
Using a written schedule (e.g. personal diary) (n=0)	0	
Heath Care Provider Related (n= 2)		22.2
Health care provider instructions (n=2)	100	
Health care provider optimism (n=0)	0	
Being involved in plan of care (n=0)	0	
Motivation Related (n=2)		22.2
Possessing sense of personal drive/motivation (n=2)	100	
Attitudes and Beliefs Related (n=1)		11.1
Thinking the medication will work (n=1)	100	
Hoping the medication will work (n=0)	0	

Table continues

Facilitator Type	% Within Facilitator Category	% Total Sample (n=9)
Cognition Related (n=1)		11.1
Ability to remember to take pills (n=1)	100	
Control Belief Related (n=1)		11.1
Possessing sense of control over circumstances (n=1)	100	
Knowledge Related (n=0)		0
Understanding how the medication works (n=0)		

Note. Total sample size = 9. Sample size varies within facilitator categories.

Secondary Research Question

What background factors and personal experiences with infertility treatment are associated perceived barriers of and facilitators to MA among women undergoing infertility treatment?

Hypothesis 4

Differences will exist in women's personal experiences with infertility treatment based on women's age, race/ethnicity, level of education, income, and infertility insurance status.

Broader themes that emerged concerning personal experiences with infertility treatment included (a) individual experiences, (b) social support experiences, and (c) treatment concern experiences. Individual experiences were categorized into (1) feelings of self-blame, (2) feelings of emotional distress, (3) feelings of psychological distress, (4) positive view on treatment success, and (5) negative view on treatment success. Social support experiences was categorized into (1) having a supportive partner, (2) having a broad support system, and (3) feeling a need for greater public awareness and open discussions regarding infertility. Treatment concern experiences were categorized into (1) concerns about health risks, (2) concerns about treatment outcomes, and (3) concerns about financial burden. Table 4.12 provides a detailed list of personal experience thematic categories with participant response percentages.

Background factor variables and the relationship to personal experiences with infertility treatment are provided with p-values in Table 4.13. Statistical significance is set at $p < 0.05$. Statistically significant values are signified with an asterisk. There was a

Table 4.12

Personal Experiences Thematic Categories Based on Data from All Participants

Personal Experiences	% Total Sample (n = 30)
Individual Experiences	
Feelings of Self Blame (n=3)	10
Feelings of Emotional Distress (n=17)	56.7
Feelings of Psychological Distress (n=11)	36.6
Positive View on Treatment Success (n=9)	30
Negative View on Treatment Success (n=8)	26.6
Social Support Experiences	
Supportive Partner (n=18)	60
Broader Support System (n=24)	80
Need for Infertility Public Awareness (n=7)	23.3
Treatment Concern Experiences	
Concerns about Health Risks (n=10)	33.3
Concerns about Treatment Outcomes (n=12)	40
Concerns about Financial Burden (n=10)	33.3

significant correlation (0.56; p= 0.049) between women's race and feelings of self-blame for having fertility problems. Caucasians and African-American women had a higher probability of reporting feelings of self-blame. Asian, Hispanic, and Native American women had a lower probability of reporting feelings of self-blame.

There was a significant correlation (0.56; p= 0.010) between number of prior failed treatment cycles and women experiencing feelings of emotional distress. Women who had reported zero to one previous failed treatment cycles had a lower probability of experiencing

Table 4.13

P-values Explaining the Relationship between Demographic Factors and Personal Experiences with Infertility Treatment

Personal Experience	Age Group	Race	Education	Income	Residential Community	Prior Child	Infertility Insurance Status	Number of Previous Failed Cycles
Individual Experiences								
Feelings of Self Blame	.369	.049*	.649	.609	.717	.361	.599	.653
Feelings of Emotional Distress	.043	.635	.237	.369	.105	.197	.373	.010*
Feelings of Psychological Distress	.711	384	.742	.121	.176	.850	.407	.985
Positive View on Treatment Success	.193	.702	.586	.092	.047*	.680	.180	.202
Negative View on Treatment Success	.909	.199	.722	.594	.631	.842	.139	.355
Social Support Experiences								
Supportive Partner	.364	.199	.108	.222	.933	.015*	.516	.385
Broader Support System	.679	.061	.526	.141	.392	.171	.331	.352
Need for Infertility Public Awareness	.799	.341	.788	.888	.424	.666	.621	.424
Treatment Concern Experiences								
Concerns about Health Risks	.574	.767	.168	.334	.223	.333	.609	.281
Concerns about Treatment Outcomes	.364	.119	.337	.710	.103	.709	.078	.601
Concerns about Financial Burden	.972	.767	.654	.381	.583	.100	.767	.193

Note. Sample size=30. P-values are based on Chi-Square Test calculations. Significance was set at 0.05.

feelings of emotional distress. Women who reported having two to three previous failed treatment cycles had a higher probability of reporting feelings of emotional distress. There was a significant correlation (0.45; p= 0.047) between women's place of residence and holding a positive view regarding infertility treatment success. Women who lived in urban and rural communities had a higher probability of having a positive outlook on treatment success. Women who lived in suburban communities had a lower probability of having a positive outlook on treatment success.

There was a significant correlation (-0.44; p= 0.015) between women who already had children and having a supportive partner. Women who had at least one prior child had a lower probability of reporting a supportive partner. Women who were childless had a higher probability of reporting a supportive partner. The correlation between having a prior child and reporting a supportive partner was -0.44. There were no significant relationships between age, ethnicity, level of income, infertility insurance status, and women's personal experiences with infertility treatment.

Hypothesis 5

Differences will exist between adherent and non-adherent women by age, race, ethnicity, level of education, income, and infertility insurance status.

There were no significant differences between women who were adherent and women who were non-adherent based on demographic factors. Table 4.14 provides background factor variables and the corresponding relationship to adherence in p-values.

Table 4.14

P-values Explaining Relationship between Background Factors and Adherence

Background Factor	Adherent versus Non-adherent (n=18)
Age Group	.767
Race	.381
Ethnicity	.303
Education	.352
Income	.301
Residential Community	.325
Prior Child	.257
Infertility Insurance Status	.574
Number of Previous Failed Cycles	.053

Note. P-values are based on Chi-Square Test calculations. Significance was set at 0.05.

Exploratory Research Question

How do women's personal experiences with infertility treatment influence MA behaviors?

Exploratory Hypothesis

Differences will exist between women who are adherent and women who are non-adherent based on women's personal experiences with undergoing infertility treatment.

Women who were adherent were significantly more likely to have a positive view on treatment success, and women who were nonadherent were more likely to not have a positive view on treatment success (0.62; p= 0.009). There were no significant differences

between the two groups of women based on other personal experiences. Table 4.15 provides participant response percentages to the thematic categories of personal experiences with infertility treatment and the relationship between women who were adherent and women who were not adherent to infertility medication.

Table 4.15

Personal Experiences Thematic Categories Based on Adherence

Personal Experiences	Total Adherent n (%)	Total Non-adherent n (%)
Individual Experiences		
Feelings of Self Blame	0 (0)	2 (22.2)
Feelings of Emotional Distress	5 (55.6)	5 (55.6)
Feelings of Psychological Distress	3 (33.3)	4 (44.4)
Positive View on Treatment Success	5 (55.6)*	1 (11.1)*
Negative View on Treatment Success	2 (22.2)	3 (33.3)
Social Support Experiences		
Supportive Partner	7 (77.8)	5 (55.6)
Broader Support System	7 (77.8)	7 (77.8)
Need for Infertility Public Awareness	2(22.2)	4 (44.4)
Treatment Concern Experiences		
Concerns about Health Risks	2 (22.2)	5 (55.6)
Concerns about Treatment Outcomes	3 (33.3)	3 (33.3)
Concerns about Financial Burden	2 (22.2)	2 (22.2)

Note. Total adherent: n=9. Total non-adherent: n=9. P-values are based on Chi-Square Test calculations. Significance was set at 0.05 indicated by *.

Post Hoc Analysis

A post hoc analysis was conducted to determine if there was a correlational relationship between women's self-report of infertility MA and their actual medication-taking behaviors.

Analysis plan. The assumption of normality was not met for the distribution of MA scores based on the small sample size (n=18) that used MEMS®. Thus Spearman's rho correlation coefficient was computed to assess the relationship between the five behavior-focused items on the ASK-20 Adherence Barrier Survey (independent variable) and MA scores (dependent variable) and the MA scores at a significance level of .05.

Higher ASK-20 Adherence Barrier Survey scores for the five MA behavior-focused items indicated a higher degree of infertility MNA. Statistical significance was set at $p < 0.05$. There was a significant negative correlation (-.49; p=.020) between participant self-report of MNA barrier scores and MA scores.

CHAPTER 5

DISCUSSION

Chapter 5 includes a robust discussion of study findings, strengths, limitations, implications for future studies, and conclusion. The purpose of the B-NFORMED study was to identify specific barriers to and facilitators of infertility MA while documenting women's actual medication-taking behaviors. This study has provided deeper insight concerning the misconception that who undergo infertility treatment are fully adherent to their infertility medication regimen. Although the median MA score of the 18 (60%) participants who used medication electronic monitoring appeared very high at 0.98, half (50%) of these women had variable MA scores that ranged from 0.75 to 0.95, and the other half (50%) of the women had a 1.00 MA score, which raised the overall MA rate. Because previous studies have not documented infertility MA scores of less than 1.00 to achieve optimal reproductive outcomes, a MA threshold score of 1.00 was chosen to divide the adherers from the non-adherers. As such, the MA adherence patterns found in this study are in alignment with known oral infertility MA behaviors (Mahoney et al., 2019) and general MA behaviors (Sabaté & World Health Organization, 2003) across broader patient populations.

Letrozole was the medication monitored in this study for 17 of 18 (94.4%) participants. Clomiphene citrate was used by only one (5.5%) participant. Both medications were prescribed once daily for a 5-day treatment course per cycle. Letrozole is a well-known treatment for breast cancer in postmenopausal women and is commonly used for infertility treatment (ovulation induction) based on its antiestrogenic properties (Kar, 2013). Clomiphene citrate is primarily used for infertility treatment (ovulation induction) and other hormonal conditions due to its antiestrogenic properties (Kar, 2013). Yet, the dose-

dependent efficacy on pregnancy rates and surrogate measures of infertility treatment effectiveness (e.g., follicular development, changes in hormone levels, cervical mucus quality, and ovulation) has not been established for either letrozole or clomiphene citrate. Prior studies have compared the uses or letrozole and clomiphene citrate for ovulation induction, although MA behaviors have not been the focus of this research (Bequm, Ferdous, Bequm, & Quadir, 2009; He & Jiang, 2011). Although pregnancy rates were not the current study outcome, examining infertility MA behaviors should be an important step to accomplishing pregnancy.

With respect to Vrijens and colleagues' (2012) proposed taxonomy for defining MA (initiation, implementation, discontinuation, and persistence), all 18 women who used the MEMS® attained successful initiation of letrozole and clomiphene citrate. None of them discontinued the medication early. However, non-adherence occurred during the implementation phase, when the women's actual dosing behaviors were not in alignment with the prescribed dosing regimen. The women were advised by the infertility providers to take the medication at the same time every day, and they were provided a two-hour window with the MEMS®. Still, all 18 women persisted through the five-day completion period for letrozole and clomid.

The entire sample (n=30) of women enrolled in the B-NFORMED study identified several barriers and facilitators to following their prescribed infertility medication regimens. More than half (53%) responded in agreement to currently feeling sad, down, or blue on the ASK-20 Adherence Barrier Survey. Depression has been shown to worsen people's medication taking patterns (Gellad, Grenard, & McGlynn, 2009). Depression and anxiety is more prevalent in women with infertility compared to women without infertility (Lakatos,

Szigeti, Ujma, Sexty, & Balog, 2017). In fact, depression and anxiety are well understood to elevate stress levels for women undergoing infertility treatment (Ogawa, Takamatsu, & Horiguchi, 2011; Prasad, Kumar, Nayar1, Prasad, & Sharma, 2017; Rooney & Domar, 2018). Furthermore, newer research has shown that higher stress levels could compromise infertility treatment outcome, which demonstrates a reciprocal process (Rooney & Domar, 2018). Thus, innovative psychological interventions have been tested and have been shown to reduce psychological distress, which has subsequently resulted in higher pregnancies rates during infertility treatment (Chow, Cheung, & Cheung, 2016; Frederiksen, Farver-Vestergaard, Skovgård, Ingerslev, & Zachariae, 2015). This raises the question if psychological interventions used in prior studies could have also positively impacted women's MA behaviors. The relationship between depression and infertility MA had not been investigated prior to this study.

All medications monitored in this study were prescribed for once daily dosing. Still, 40% (n=12) of the 30 total participants responded that taking medication more than once per day was a barrier to MA. This raises suspicion that women may have considered additional prescribed medications when taking the ASK-20 Barrier Adherence Survey although the PI instructed participants to concentrate solely on infertility medications. Seventeen percent (n=5) of women reported concern about medication affecting sexual health as a barrier, substantiating prior literature that women receiving infertility treatment experience difficulties with their sexuality (Tao, Coates, & Maycock, 2011).

When comparing group differences with perceived barriers, women who were adherent to their infertility MA regimen had significantly (p=0.019) higher MA barrier scores compared to women who were non-adherent (39 versus 30). Yet, the mean MA

barrier score (34.5) on the ASK-20 Adherence Survey did not approach the maximum score (100) on the total barrier score continuum. Nonetheless, women with a perceived higher degree of barriers had significantly ($r = -.49$, $p=0.020$) lower MA rate compared to women with a perceived lower degree of barriers—yielding a negative correlation with a large effect size of 0.24. These findings are analogous to previous studies that used the ASK-20 Adherence Survey to assess MA barriers and MA patterns in other patient populations (Martza et al., 2008; Rolnick, Asche, Pawloski, Bruzek, & Hedblom, 2013). In patients with asthma, for example, Atsuta et al. (2017) found a high correlation of -.51 between mean ASK-20 Adherence Barrier Survey total scores and MA scores with a much larger sample size (n= 290) than the B-NFORMED study.

Women enrolled in the current study cited a host of facilitators to infertility MA, while the majority (60%) cited physical aid related factors (e.g., placing pills where easily visible, using a medication cabinet or pill box, using a mobile phone alarm). The other most common facilitators reported were routine (50%), social support (43%), and motivation related (27%). Nevertheless, the relationship between the number and types of facilitators reported by women were not significant when correlated with their corresponding MA scores.

This finding raises inquiry if MA facilitators in this population could be highly individualized in magnitude and effect on adherence behaviors, such that grouping women by common facilitators may have been a more daunting task than conceptualized. This may explain the absence of psychometrically sound instruments in the literature that capture the construct of MA facilitators like that of MA barrier scales. Accordingly, qualitative methods have been traditionally employed to investigate people's perceived facilitators to MA

highlighting the uniqueness that each participant offers when generating this type of study data (Castro et al., 2015; Claes et al., 2014; Curioso et al., 2010; Ho et al., 2017).

Background factors such as age, race, education, income, and health insurance status have influenced medication-taking behaviors in various patient populations (Cho & Kim, 2014; Conn et al., 2015; Conn, Ruppar, Enriquez, & Cooper, 2015; Kilgore et al., 2016; Park, Howie-Esquivel, & Dracup, 2014; Whittle et al., 2016). In the B-NFORMED study, there were no significant demographic differences found in relation to MA behaviors, yet samples demographics were largely homogeneous. Concerning presence of insurance coverage and out-of-pocket expenses for infertility treatment services, all (96.7%) but one (3.3%) participant reported either having partial responsibility or bearing full out-of-pocket pay responsibility. Therefore, discriminating between demographic variables of women who were adherent and who were non-adherent was a difficult task, although the sample demographics are in alignment with national statistics for this population (Kessler, Craig, Plosker, Reed, & Quinn, 2014).

Medication cost was not a cited barrier to MA based on women's responses on the ASK-20 Adherence Barrier Survey. This could have occurred based on the fact that oral medications (letrozole and clomiphene citrate) are modestly priced compared to injection medications. In addition, infertility treatment involves an array of other services that are independent of medication costs (e.g., laboratory tests, transvaginal ultrasounds, intrauterine insemination procedure) (ASRM, 2012b). Furthermore, if infertility treatment progresses to more advanced modalities such as IVF, the associated costs can steeply skyrocket (Katz et al., 2011). During the structured interviews when women in the current study were asked about treatment concerns, 10 (33.3 %) of them cited financial burden.

Social support and health care provider support were assessed as both barriers and facilitators in the B-NFORMED study. The literature has classified social support into two types: (a) structural support (e.g., marital status, living arrangement) and (b) functional support—which is further differentiated into instrumental/practical support (e.g., picking up prescriptions, reading labels) and emotional support (e.g., encouragement, listening) (DiMatteo, 2004; Scheurer, Choudhry, Swanton, Matlin, & Shrank, 2012). Of the total 30 participants, all were married and cohabited with their spouses. Only one (3.3%) woman cited inadequate help from others with medication-taking. Thirteen (43.3%) participants reported instrumental and emotional type support with medication-taking behaviors, and women without children were significantly ($p=0.015$) more likely to report having a supportive partner compared to women who already had a child. However, no significant differences were found between women who were adherent and women who were non-adherent to their infertility medication with respect to social support.

Women undergoing infertility treatment have reported a preference to shared decision-making with their health care provider (Boivin et al., 2012). In the B-NFORMED study, the majority of participants reported positive health care provider related support-based responses to the ASK-20 Adherence Barrier Survey and structured interviews. Nonetheless, four (13.3%) participants felt neutral concerning working with the health care provider in making shared decisions. Still, no significant differences were found between women who were adherent and women who were non-adherent to their infertility medication with respect to health provider support.

Infertility treatment takes an emotional toll on women (Gameiro et al., 2015). In the current study, Caucasian and African-American women were more likely to report feelings

of self-blame for having infertility compared to Asian, Hispanic, and Native American women. However, since the majority of participants were Caucasian, which served as the reference (nominal) variable for race in the analysis, caution should be taken when interpreting these findings for non-Caucasian women. Interestingly, regardless of race, research has shown that infertility treatment is associated with higher levels of emotional distress than having the infertility diagnosis itself (Greil, McGuillan, Lowry, & Shreffler, 2011). Women in the current study who experienced prior failed treatment cycles were significantly ($p=0.010$) associated with experiencing feelings of emotional distress.

Women's personal experiences with infertility treatment has been shown to impact their decisions about treatment discontinuation (Domar et al., 2018; Gameiro et al., 2012; Gameiro et al., 2013). Seven (23.3%) participants in the B-NFORMED study decided to either suspend or discontinue infertility treatment. Early treatment discontinuation is generally considered a primary determining factor of treatment ineffectiveness, yet many women choose to discontinue infertility treatment, including women with infertility insurance coverage (Domar et al., 2018; Gameiro et al., 2012). Although there are no clear indicators for infertility treatment discontinuation, treatment rejection has been considered a possible causative factor for some women (Gameiro et al., 2012; Gameiro et al., 2013; Olivius et al., 2004). In the current study, women who lived in suburban communities and women who were non-adherent to their infertility treatment regimen were less likely to have a positive view on treatment success. These findings raise speculation if women's level of enthusiasm concerning treatment outcomes influences their decision to discontinue treatment. Moreover, the relationship between infertility treatment outcomes, early treatment

discontinuation, and MNA will be of particular interest when developing future interventions.

Advances in healthcare research and treatment ingenuity have contributed to a paradigm shift that emphasizes customized treatment based on individuals' needs (Agyeman, Ofori-Asenso, 2015; Vogenburg, Barash, & Pursel, 2010). Because many treatment modalities incorporate prescription medications, researchers have now directed attention at understanding determinants of MA and identifying predictors of MA (Kardas, Lewek, & Matyjaszczyk, 2013). Prediction of MA behavior remains a challenge for two reasons: (1) multifaceted determinants of MA are present, and (2) the factors surrounding these determinants vary among populations (e.g., senior adults, female hormonal contraception, individuals with HIV, diabetes, and hypertension) (Kardas et al., 2013; Kazerooni, Takizawa, & Vu, 2014; Kirkman et al., 2015; Krousel-Wood, Muntner, Islam, Morisky, & Webber, 2009; Rodgers et al., 2018; Thames et al., 2012). Thus, identifying determinants and predictors of MA among women with infertility may be an additional challenge.

Strengths

This novel study used a mixed methods approach to identify what women perceived as barriers to and facilitators of infertility MA. The mixed methods methodology synergized interview data with questionnaire data to generate new knowledge in reproduction science. Infertility medication-taking patterns were followed with the MEMS® instrument to determine if individual differences in perceived barriers and facilitators between women influenced their actual behaviors. The use of the MEMS® instrument offered a highly reliable and valid means to determine at which phase (initiation, implementation, and

discontinuation) infertility MNA occurred. Because little is known concerning how the burden of having infertility and undergoing infertility treatment impacts subsequent MNA, the B-NFORMED study offers a unique foundation for future investigation.

Limitations

Several factors limited generalizability of the study findings. The setting was a single site practice, whereas multiple clinics could have broadened participant recruitment. The study sample was largely homogenous. All participants were married and the majority were Caucasian, college-educated, and lived in suburban communities. Only 18 (60%) of 30 women used the MEMS®, compromising the study's power to discriminate true differences in barrier and facilitator variables between women who were adherent and women who were non-adherent. The convenience sampling approach increased opportunity for sampling bias. Selection bias was a concern because there was no means to determine demographic differences between those who participated in the study and those who declined participation. Lastly, there is uncertainty about the degree to which women responded to ASK-20 Adherence Barrier Survey items based on other prescription medications additional to infertility medication.

Implications for Future Research

The findings of the B-NFORMED study have theory, research, practice, and policy implications. Fishbein and Ajzen's (2010) Reasoned Action Model purports that perceived barriers to and facilitators of performing a behavior can impact one's intention to perform that behavior. In accordance with this theory, the B-NFORMED study demonstrated that a greater amount of perceived barriers to infertility MA influences women's medication-taking behaviors. Yet, there is still uncertainty about how perceived MA facilitators impact

infertility MA. Future studies are needed to determine the type and magnitude of facilitators that could influence women's intention to adhere to prescribed infertility medication regimens. Understanding the relationship between infertility treatment discontinuation and MNA will be important. Also, theory-driven investigations will be beneficial to explain determinants and predictors of infertility MA. Further, interventions that implement counseling methods such as motivational interviewing should be considered to reduce women's psychological and emotional distress, and improve MA during infertility treatment cycles.

The B-NFORMED study revealed oral MNA behaviors with merely once a day medication dosing schedules. Future research should concentrate on oral and injection MA patterns during IUI and IVF cycles when medication schedules become more complex, which could elevate the risk for infertility MNA. Moreover, based on the post hoc analysis of this study, which significantly correlated women's self-report of MA with their actual infertility medication-taking patterns, implementation of a brief MA assessment in clinical practice could identify those needing assistance to improve their MA behaviors. Additional studies are needed to fully understand how infertility non-adherence behaviors affects pregnancy outcomes. The development and testing of innovative interventions will be necessary to overcome MNA not only in practice but during future clinical trials that evaluate the treatment effectiveness of new and existing infertility medications. Non-adherence behaviors during infertility medication clinical trials compromises study power, reduces treatment effect size, and weakens overall study findings.

In this era of personalized medication, more research is focused on tailoring infertility pharmacotherapies to women based their genetic characteristics to optimize

treatment outcomes (Kalinderi, Asimakopoulos, Nikolettos, & Manuolopulos, 2018). Still, the benefits of these therapies are dependent upon women's adherence to the regimen. Future studies are needed that incorporate women's personal needs into clinical trials and clinical practice guidelines. In the B-NFORMED study, women frequently reported feelings of psychological and emotional burden while undergoing infertility treatment. Gaining knowledge about how treatment burden influences infertility medication-taking can assist health care providers with making better treatment decisions.

With advancements in reproduction science, women who would ordinarily remain childless have been able build families. Yet, there are many women who do not have access to infertility treatment due to lack of a covered benefit for these services. Meanwhile, national policy discussions remain in debate concerning expansion for infertility services in the U.S. The majority of women in the B-NFORMED study did not have full health insurance coverage for infertility treatment services. Several of them reported that treatment cost was a major concern, particularly if treatment had progressed to IVF. Therefore, future studies testing cost-effective interventions to improve women's infertility MNA could influence lawmakers' decisions for implementing new policies that mandate infertility insurance coverage options to women nationwide.

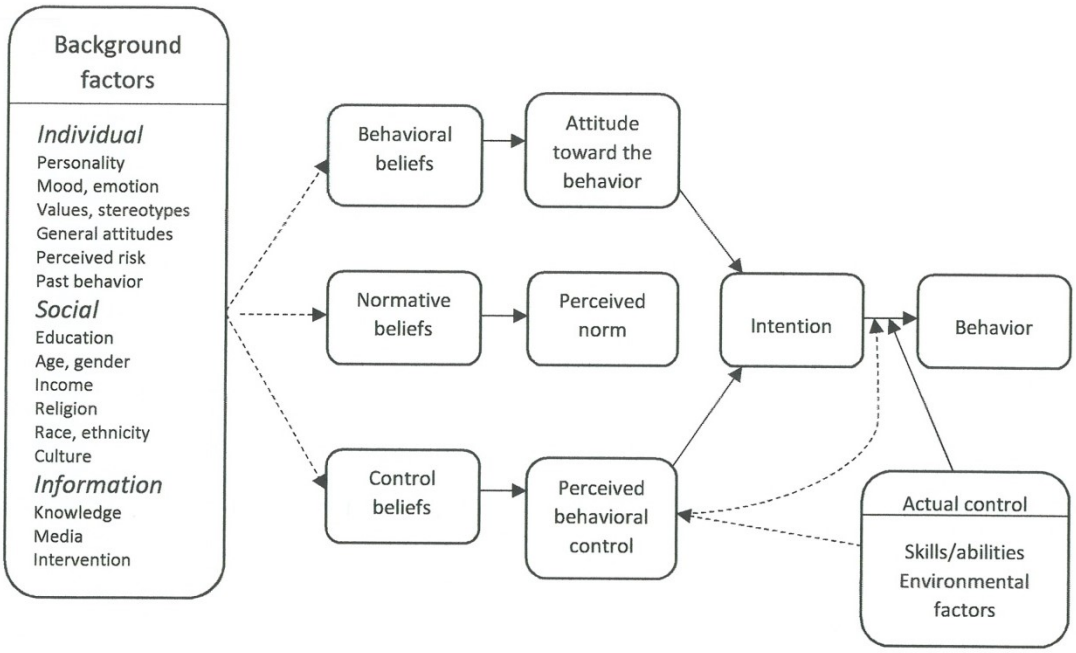
Conclusion

The B-NFORMED study has identified women's perceived barriers to and facilitators of MA while undergoing infertility treatment and described those that were associated with women's actual MA behaviors. The findings of this study offer new insight about this unique population that could impact the future of clinical practice. This study

serves as a framework to cultivate ongoing scientific discovery including forthcoming interventional studies aimed at optimizing infertility MA behaviors.

APPENDIX A

FISHBEIN AND AJZEN'S REASONED ACTION MODEL



(Fishbein & Ajzen, 2010)

This model asserts that intention determines the likelihood of behavior performance.

- Background factors are considered to influence how information is recalled and interpreted, which impacts beliefs about performing a behavior.
- Behavioral beliefs are assumed to regulate an individual's attitude toward performing a behavior.
- Normative beliefs are purported the extent to which important people in one's life would approve or disapprove of a behavior being performed.
- Control beliefs are perceived personal and environmental factors that inhibit (barriers) or help (facilitators) the likelihood of performing a behavior.
- Action control is based on realistic insufficient abilities, skills, and environmental constraints that could prevent an individual from acting on intention to perform a behavior.
- Intention is indicative of one's willingness or readiness to implement a behavior.
- Behavior is a person's level of performance to achieve a designated outcome.

APPENDIX B

LETTER OF SUPPORT

Reproductive Resource Center
Experience. Innovation. Hope.

April 17, 2018

Diane Mahoney
Ph.D. Student
University of Missouri-Kansas City
Kansas City, Missouri 64080

Dear Diane:

I am pleased to offer my support for your dissertation study, "Barriers to and Facilitators of Infertility Medication Adherence: A Mixed Methods Study." As the Medical Director of Reproductive Resource Center, I believe this research proposal is both timely and important in the field of Reproductive Medicine. Determining the patterns and predictors of medication non-adherence and implementing strategies to reverse this undesirable behavior is very important to maximize the effectiveness of our innovative assistive reproductive technology procedures. I provide you access to conduct your study at Reproductive Resource Center and I whole heartily offer my support for your compelling work.

Sincerely,

Celeste Brabec, MD
Fellow of the American College of Obstetrics and Gynecology
Board Certified, Obstetrics and Gynecology and Reproductive Endocrinology and Infertility
Medical Director
Reproductive Resource Center
12200 West 106th Street, Suite 120
Overland Park, KS 66215
913-894-2323

12200 W. 10 6th St., Suite 120 • Overland Park, Kansas 66215
(913) 894-2323 • fax (913) 894-0841 • rrc.com

APPENDIX C

DEMOGRAPHIC QUESTIONNAIRE

1. **Age:** _____ **Date** _____

2. **Marital Status ("X" ONLY one with which you MOST CLOSELY identify):**

   ☐ Married
   ☐ Single
   ☐ Divorced
   ☐ Widowed

3. **Race ("X" ONLY one with which you MOST CLOSELY identify):**
   ☐ American Indian or Alaska Native
   ☐ Asian
   ☐ Black or African-American
   ☐ Hispanic or Mexican American
   ☐ Native Hawaiian or Other Pacific Islander
   ☐ Non-Hispanic White

4. **Ethnicity ("X" ONLY one with which you MOST CLOSELY identify):**

   ☐ Hispanic or Latino
   ☐ Not Hispanic or Latino

5. **Which type of community to do you live in? ("X" ONLY one with which you MOST CLOSELY identify):**
   ☐ Suburban
   ☐ Urban
   ☐ Rural

6. **How would you describe you level of infertility insurance coverage? ("X" ONLY one with which you MOST CLOSELY identify):**

   ☐ All self-pay
   ☐ Partial out-of-pocket
   ☐ Full coverage

7. **Which category below best describes your household income? ("X" ONLY one with which you MOST CLOSELY identify):**

   ☐ Less than $50,000
   ☐ $50,000 - 74,999
   ☐ $75,000 - $99,999
   ☐ $100,000 - $124,999
   ☐ $125,000 - $ 149,999
   ☐ More than $150,000

8. **Which category below best describes your highest of education? ("X" ONLY one with which you MOST CLOSELY identify):**

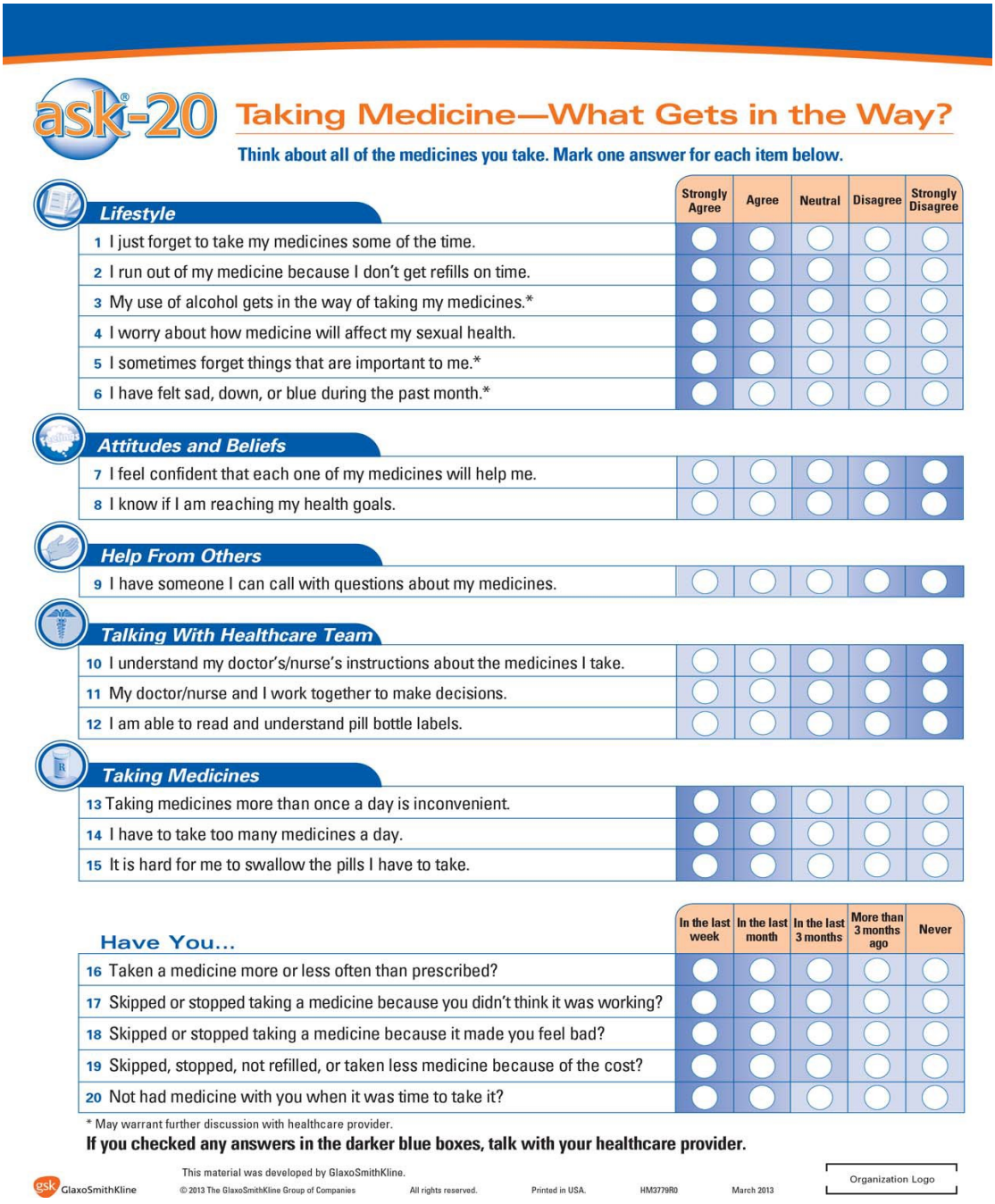
- ☐ Less than high school
- ☐ Some high school, no diploma
- ☐ High school graduate, diploma or the equivalent (for example: GED)
- ☐ Some college, no degree
- ☐ Associate degree
- ☐ Bachelor's degree
- ☐ Master's degree
- ☐ Doctorate degree

9. **Please <u>list below</u> the name, dose, and frequency of the infertility medication(s) that you are currently taking?**

Name of Medication	Prescribed Dose	How many times per day?

APPENDIX E

ASK-20 ADHERENCE BARRIER SURVEY



ask-20 Taking Medicine—What Gets in the Way?

Think about all of the medicines you take. Mark one answer for each item below.

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
Lifestyle					
1 I just forget to take my medicines some of the time.	○	○	○	○	○
2 I run out of my medicine because I don't get refills on time.	○	○	○	○	○
3 My use of alcohol gets in the way of taking my medicines.*	○	○	○	○	○
4 I worry about how medicine will affect my sexual health.	○	○	○	○	○
5 I sometimes forget things that are important to me.*	○	○	○	○	○
6 I have felt sad, down, or blue during the past month.*	○	○	○	○	○
Attitudes and Beliefs					
7 I feel confident that each one of my medicines will help me.	○	○	○	○	○
8 I know if I am reaching my health goals.	○	○	○	○	○
Help From Others					
9 I have someone I can call with questions about my medicines.	○	○	○	○	○
Talking With Healthcare Team					
10 I understand my doctor's/nurse's instructions about the medicines I take.	○	○	○	○	○
11 My doctor/nurse and I work together to make decisions.	○	○	○	○	○
12 I am able to read and understand pill bottle labels.	○	○	○	○	○
Taking Medicines					
13 Taking medicines more than once a day is inconvenient.	○	○	○	○	○
14 I have to take too many medicines a day.	○	○	○	○	○
15 It is hard for me to swallow the pills I have to take.	○	○	○	○	○

Have You...	In the last week	In the last month	In the last 3 months	More than 3 months ago	Never
16 Taken a medicine more or less often than prescribed?	○	○	○	○	○
17 Skipped or stopped taking a medicine because you didn't think it was working?	○	○	○	○	○
18 Skipped or stopped taking a medicine because it made you feel bad?	○	○	○	○	○
19 Skipped, stopped, not refilled, or taken less medicine because of the cost?	○	○	○	○	○
20 Not had medicine with you when it was time to take it?	○	○	○	○	○

* May warrant further discussion with healthcare provider.

If you checked any answers in the darker blue boxes, talk with your healthcare provider.

GlaxoSmithKline

This material was developed by GlaxoSmithKline.

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Organization Logo

APPENDIX E

PERMISSION TO USE ASK-20 ADHERENCE BARRIER SURVEY

April 2, 2018
Via Email to

Diane Mahoney
PhD Nursing Student
University of
Missouri-Kansas
City
descg5@mail.umkc.
edu

RE: Permission to use The Adherence Starts with Knowledge Surveys

(ASK-12 and ASK-20)

Dear Ms. Mahoney,

Thank you for your email of March 20, 2018 requesting permission to use the Adherence Starts with Knowledge Survey (ASK-12 and ASK-20) (the "Instrument") in English. We understand you are interested in using the Instrument as part of your dissertation research at the University of Missouri-Kansas City to investigate barriers to medication adherence among women who are undergoing infertility treatment.

GlaxoSmithKline is pleased to grant you permission to use, reproduce and distribute paper and electronic pdf copies of the Instrument in English as part of the above clinical study, subject to the following conditions:

1. You may not modify the Instrument or combine it with other instruments without prior written approval;
2. You must use the Instrument in its entirety, with the questions appearing verbatim and in order;
3. You must not remove any trademark ownership statements or copyright notices that appear on the Instrument;
4. You must use the Instrument only for the specific purposes stated in your request;
5. You must use only the most current version of the Instrument, which, for ease of reference, is enclosed with this letter (current as of the date of this letter).

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permission granted herein prior to such revocation. Please be advised that we cannot make, and hereby disclaim, any representations or warranties about this Instrument, including any warranties as to additional permissions that may be required for its use. Thank you for your interest in GlaxoSmithKline. If you have any questions regarding this matter, please contact me at your convenience.

Sincerely,

Matthew S Lau, PharmD, MSCR
Manager, US Value, Evidence & Outcomes US
Medical Affairs
GlaxoSmithKline

APPENDIX F

INTERVIEW GUIDE

Facilitators of Medication Adherence
Opening Statement: There are certain ways people are told to take these medicines. For example, take a certain number of pills or injections at a certain time of day.

Describe to me how you are taking your medications?

What helps you take your infertility medicine?

Is there something that anyone else says or does that helps you to continue taking infertility medication? If so, please describe.

If you were uncertain about whether you are taking your infertility medicine correctly, what would you do?

Personal Experiences with Infertility Treatment
Transition Statement: Many women choose to receive infertility treatment and each person's experience with infertility treatment is unique.

Think about you—without thinking about anyone else. *What impact has receiving infertility treatment had on you as a person, I mean your thoughts, feelings, personal characteristics, and personal circumstances?*

Now, think about people in your life. *How has your infertility treatment influenced the actions, reactions, and attitudes of these people?*

What are your personal concerns about receiving infertility treatment?

Closing Question
Is there anything else you would like to add about your experience with infertility medication or infertility treatment?

APPENDIX G

MEDICATION EVENT MONITORING SYSTEM® (MEMS)

WestRock

MEMS® 6
Medication Event Monitoring System

	MEMS® 6 SmartCap (with LCD display)	MEMS® 6 TrackCap (without LCD display)
Housing type A		
Housing type B (child resistance capability)		

The monitor

MEMS 6 is an electronic monitoring system designed to compile the dosing histories of ambulatory patients prescribed oral medications. The system is comprised of two parts: a standard plastic vial with threaded opening and a closure for the vial that contains a micro-electronic circuit that registers dates and times when the closure is opened and when it is closed.

The results

Time-stamped medication events stored in the MEMS 6 can be transferred at any time through the MEMS Reader to a MS-Windows-based computer. WestRock software analyzes and displays or prints in various formats the computed parameters of the patient's adherence. The results are now widely regarded as the gold standard measure of patient adherence to medications.

Key points

- Available in 38mm, 42mm and 45mm thread diameters
- Optional LCD display
- Optional child resistance functionality
- Service life: 36 months from shipment
- Water resistant
- Data transfer by patented wireless inductive coupling
- CE marked
- Non-volatile memory for data storage (maintains data integrity for years after loss of battery power)
- Optimal events detection technology

Version 2.6

Technical specifications

Clock precision	+/- 90 seconds per month
Event resolution	30 seconds
Memory capacity	> 3500 events
Service life	36 months
Thread	38 mm – Neck Finish 38-400 42 mm – Neck Finish 42-400 45 mm – Neck Finish 45-400
Vials	Available in sizes from 60 cc to 1050 cc
Material of the plunger and protection cap (see image below)	High Density Polyethylene (HDPE) for Pharmaceutical/Medical applications Certificate of compliance is provided with MEMS 6 delivery
Material of the external housing (see image below)	Acrylonitrile Butadiene Styrene (ABS)
Degree of permeation	Water resistant (designed to resist but not entirely prevent the penetration of water)
Identification	Unique 6 digits serial number hard coded in the memory and printed on the bottom of the monitor

LCD Display - optional

The number in the center of the LCD indicates the number of openings of the vial since 3 AM. It will be reinitialized every 24 hours (at 3 AM). After more than 9 daily openings, the digit "9" will blink. The 12 bars in a circle around the central number indicate the number of hours that have passed since the last opening. Each bar represents one hour. From the 13th hour, the corresponding bars will flash. After more than 24 hours, all 12 bars flash. They all disappear when the vial is next opened.

1 opening since the beginning of the day
4 hours passed since the last opening

1 opening since the beginning of the day
16 hours passed since the last opening

When the vial has not been opened for more than 168 hours (one week), the LCD display is automatically turned off, to conserve battery power. The display is reactivated, however, when the vial is next opened.

Child Resistance (CR) - optional

The MEMS 6 is available with child resistant closure based on "push down and turn" principle.

The MEMS 6 CR fulfill US C.F.R. Title 16, Part 1700 (child resistance and senior-friendliness). Tests have been performed by Perritt Laboratories Inc. in Hightstown, NJ.

Precautions

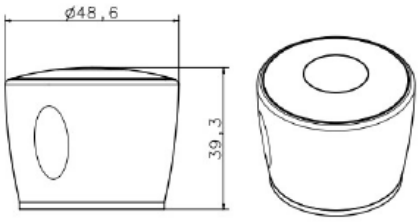
- Use with temperature between 4°C and 40°C
- Use with solid dosage forms
- Securely tighten the monitor onto the bottle
- Do not immerse in water or other liquids
- Do not use after the expiration date of the battery

Remarks

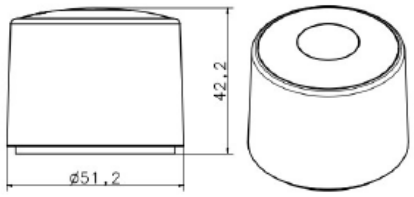
- The MEMS 6 monitor is intended to be used by only a single patient and a single drug
- The MEMS 6 monitor has been designed to withstand normal use in the home
- Improper use can result in the loss of data or product damage
- The MEMS 6 monitor is a sealed unit with no user serviceable or replacement parts

External housing dimension (in mm)

Housing type A



Housing type B



Product selection matrix

Desired features			Product order informations		Characteristics
Thread	Child resistance	LCD	Art. #	Art. Designation	Housing type
38mm Neck Finish 38-400	No	No	1020-01	MEMS6 TrackCap 38mm	A
		Yes	1020-02	MEMS6 SmartCap 38mm	
	Yes	No	1021-01	MEMS6 TrackCap 38mm CR	B
		Yes	1021-02	MEMS6 SmartCap 38mm CR	
42mm Neck Finish 42-400	No	No	1022-01	MEMS6 TrackCap 42mm	
		Yes	1022-02	MEMS6 SmartCap 42mm	
	Yes	No	1023-01	MEMS6 TrackCap 42mm CR	
		Yes	1023-02	MEMS6 SmartCap 42mm CR	
45mm Neck Finish 45-400	No	No	1024-01	MEMS6 TrackCap 45mm	
		Yes	1024-02	MEMS6 SmartCap 45mm	
	Yes	No	1025-01	MEMS6 TrackCap 45mm CR	
		Yes	1025-02	MEMS6 SmartCap 45mm CR	

Contact

WestRock Switzerland Ltd.
Avenue de la Gare 29
CH – 1950 Sion

✆ +41 27 324 78 80
✆ +41 27 324 78 81 (customer service)

Fax +41 27 323 40 62

Web
www.mwvaardex.com

WestRock

APPENDIX H

MEDICATION EVENT MONITORING SYSTEM® (MEMS) DIARY

Subject Number:_____

Write down any time that you accidentally open the MEMS®, if you don't get the MEMS® cap on tight, if you remove pills before time to take them, or any other situation that you think we should know about. This is very important so that we know when your MEMS® may have been opened when you didn't take a pill. This diary will need to be returned to us when you return your MEMS® caps.

Date	Time	Explanation of what happened

APPENDIX I

DEFERMENT OF HUMAN SUBJECTS REVIEW TO UMKC IRB

Reproductive Resource Center
Experience. Innovation. Hope.

August 29, 2018

Dear Diane Mahoney,

To protect the safety and privacy of the patients at Reproductive Resource Center while conducting your research study titled, *"Barriers to and Facilitators of Infertility Medication Adherence: A Mixed Methods Study",* I am pleased to defer human subjects review to the UMKC Institutional Review Board (IRB). I understand that UMKC IRB will thoroughly review your study, grant permission to proceed, and provide ongoing oversight of your study.

Sincerely,

Celese Brabec, MD
Fellow of the American College of Obstetrics and Gynecology
Board Certified, Obstetrics and Gynecology and Reproductive Endocrinology and Infertility. Owner and Medical Director
Reproductive Resource Center 12200 West 106th Street, Suite 120 Overland Park, KS
913-894-2323

APPENDIX J

MEDICATION EVENT MONITORING SYSTEM® (MEMS) FOLLOW-UP TELEPHONE CALLS

Subject Number:_____

Month #1/ Date_____

Do you have any questions about using the MEMS® or MEMS® diary? Tell me about how you are using them.

Month#2/ Date_____

Do you have any questions about using the MEMS® or MEMS® diary? Tell me about how you are using them.

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VITA

Diane Elaine Mahoney was born November 11, 1971, in Kansas City, Kansas. She was educated at Schlagle High School in Kansas City, Kansas. She then pursued undergraduate studies and was awarded a Bachelor of Science in Nursing degree in 1995 from the University of Kansas in Kansas City, Kansas. Shortly after graduation, Dr. Mahoney began working a Registered Nurse on a medical-oncology unit at Bethany Medical Center in Kansas City, Kansas.

Dr. Mahoney continued to pursue her education and attained a Women's Health Care Nurse Practitioner Certificate from the University of Texas Southwestern in Dallas, Texas and a Master of Science in Nursing as a Family Nurse Practitioner from the University of Kansas. She has worked in acute, ambulatory, and community-based health care settings. Most of her advanced practice nursing career has focused on promoting and improving healthy behaviors among women.

Through attainment of a Doctor of Nursing Practice, Dr. Mahoney began to embrace her role as a key stakeholder for improving health care through leadership and health care advocacy while engaging in evidence-based practice. She further subspecialized as a Nurse Practitioner in the area of Reproductive Endocrinology and Infertility to synergize her role as researcher and practitioner. Dr. Mahoney is currently a Clinical Assistant Professor at the University of Kansas School of Nursing with a career goal to conduct long-term research as a fully tenured professor.