



Medication Adherence Among Women Undergoing Infertility Treatment: A Systematic Review

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Abstract

Objectives: The present study aimed to investigate medication adherence awareness among women undergoing infertility treatment.

Materials and Methods: Several databases were searched including PubMed, Embase, CINAHL, PsycINFO, as well as ProQuest dissertations in order to collect the required data. In addition, based on the purpose of the study, English-language prospective, retrospective, observational, cross-sectional, quasi-experimental, and randomized controlled trial studies were selected which focused on medication adherence as a primary or secondary outcome in women with a diagnosis of infertility. Finally, critical appraisal for the quality of the study was assessed using Downs and Black Quality Checklist (1998) and STROBE guidelines.

Results: Three studies conducted during 1993-2011 were analyzed. Further, sample sizes varied from 30 to 626 subjects with average rates of oral medication adherence ranging from 26% to 81% when used as the first-line therapy. More frequent daily dosing was associated with lower adherence rates. Based on the results, adherence was significantly lower when women were concerned about the side effects of medication adherence or reported 3 or more side effects rather than one or 2 cases. Furthermore, women with a body mass index of $<23 \text{ kg/m}^2$ or those who viewed medical treatment as convenient had higher adherence rates. It is noteworthy that none of the studies evaluated medication adherence during controlled ovarian hyperstimulation (COH) cycles, along with intrauterine insemination (IUI) or in vitro fertilization (IVF).

Conclusions: In general, rates of oral medication adherence are found suboptimal when used alone as first-line therapy. Accordingly, further studies regarding medication-taking behaviors are warranted in future research trials involving injection medications and COH cycles associated with IUI and IVF cycles in order to strengthen the clinical practice.

Keywords: Medication Adherence, Infertility, Fertility, In vitro Fertilization

Introduction

Infertility is a significant health problem for women, which is estimated to affect 80 million people worldwide (1,2). In the United States, approximately 16% of the women of childbearing age are affected by infertility (3). In addition, many women undergo infertility treatment and are highly motivated to become pregnant (4). Infertility treatment incorporates a variety of modalities to help women achieve pregnancy from minimally invasive to highly invasive procedures, along with fertility medication. According to American Society of Reproductive Medicine (5), treatment regimens can incorporate oral and/or injection medication for controlled ovarian hyper stimulation (COH) in combination with or without intrauterine insemination (IUI), as well as assisted reproductive technology (ART) procedures such as vitro fertilization (IVF).

Women who tend 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 and marijuana cessation, and alcohol restrictions) and follow the prescribed protocols for fertility drugs in order to increase the chances of treatment success (6-10). However, adhering

to lifestyle changes recommended by the health providers are found to be problematic (9,11-14). In fact, negative lifestyle behaviors contributed to lower pregnancy rates for women undergoing IVF (15-20). This raises concerns regarding the extent to which women adhere to fertility medications while receiving the treatment.

Adherence to the prescribed medication is important for achieving the targeted health outcomes (21). Medication non-adherence is recognized as a prevalent global problem among the general population with adherence rates 50% on average, worldwide (22). Further, the medication-taking behavior of women receiving infertility treatment has not been adequately assessed. This is probably due to the belief that medication adherence is optimal in this patient population, particularly with high stakes procedures like IVF. In general, infertility treatment resulted in successful pregnancies for many women although most often after the repeated treatments. Although a woman's likelihood of pregnancy with infertility treatment decreases as she ages (35 years and older), younger women (under 35 years) undergoing assisted reproductive technology (ART) in the United States average 38% of pregnancy rates (U.S.) for each treatment cycle (23,24). Infertility treatment

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regimens are frequently complex and can impede women's daily lives (25). Treatment cycles incorporate oral and/or injection routes. Medication schedules range from daily to multiple daily doses which are essentially very time sensitive (26). Failure to correctly take the medication during a treatment cycle decreases the likelihood of the medication which has its intended effect on reproductive hormones and ovarian follicular development, ultimately drives up the healthcare costs for the repeated treatments (27,28).

Adherence can be defined as "the extent to which a person's behavior (i.e., taking medication, following a diet, and/or executing lifestyle changes) corresponds with the agreed recommendations from a health care provider" (22). In infertility literature, medication adherence is not well-defined during non-ART cycles such as IUI. With respect to ART, adherence is referred to the continuation of ART cycles including medication adherence recommended by the infertility provider until pregnancy is attained or there are provider suggestions to discontinue the treatment (29). Therefore, the existing research concentrated on ART cycle discontinuation rates rather than medication-taking patterns (29,30).

Medication adherence has 3 distinct components including initiation, implementation, and discontinuation (21). Initiation is when a patient receives the first dose of a prescribed medication. Furthermore, Implementation refers to the degree to which the patient's actual medication usage corresponds to the prescribed medication regimen. Finally, discontinuation occurs when the next scheduled dose 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 (21).

Women with infertility are a population challenged by physical, psychological, emotional, and financial demands which accompany treatment, and some women report incorrect fertility medication-taking (27,31-33). However, researchers have not yet established a methodological process to monitor medication adherence with this group of women. Nor has there been attention directed toward 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. Accordingly, the current review aimed to determine the rates of medication adherence in women undergoing assistive reproductive treatment. The study questions included *What are the rates of adherence to fertility drugs?* and *What are the predictors of and barriers to medication adherence among women receiving infertility treatment?* Clinical interventions are believed to strengthen through identifying the patterns, predictors, and barriers related to medication adherence in women with infertility. Additionally, improving the quality of future research regarding medication adherence

can have several advantages including improving clinical outcomes of the treatment, decreasing the likelihood of repeated failed cycles for non-adherence, and ultimately, reducing the overall expenditure of the health care.

Methods

Literature Search Strategy

A systematic review was conducted based on the standards of preferred reporting items for systematic reviews and meta-analysis (PRISMA) developed by Moher et al (34). To this end, a search was conducted to identify studies in which medication adherence was investigated among infertile women undergoing infertility treatment. Accordingly, several international databases were browsed including PubMed (1940-2017), Embase (1980-2017), CINAHL (1982-2017), PsycINFO (1806-2017), along with ProQuest dissertations. In addition, combinations of the following terms were used in this regard: "adherence", "compliance", "persistence", "concordance", "nonadherence", "non-adherence", "noncompliance", "non-compliance", "infertile*", "fertile*", "subfertile*", "infecund*", "subfecund*", "barren", "sterility", "infertility treatment", "fertility treatment", "in vitro fertilization", "intrauterine insemination", "pharmaceutic*", "prescript*", "medical*", "medicine", "medicines", "drug", "drugs", "women", and "female".

Inclusion/Exclusion Criteria

Inclusion criteria were prospective, retrospective, observational, cross-sectional, quasi-experimental, and randomized controlled trial studies in which female participants aged 18-44 years were investigated who were diagnosed with infertility based on their medical record. Further, such studies were selected based on their results which were related to medication adherence as the primary or secondary outcome. Furthermore, participants aged 18-44 were included since this age range is representative of those women who seek infertility treatment (4). However, According to American Society of Reproductive Medicine (5), other women were excluded since they were neither a population seeking infertility services (<18) nor were they suitable candidates for examination due to the reduction in their reproductive potential (>44) Moreover, non-English studies were excluded. The PRISMA Flow Diagram concerning the process of study selection is displayed in Figure 1. It should be noted that there was no need to obtain formal approval by an ethical review committee to conduct this review.

Data Extraction

The data extraction included author/year/design, purpose, sample/setting, intervention, measures, results, strengths, and limitations and was agreed upon by 2 independent reviewers (i.e., a DM and a CR) using a structured data collection sheet. A summary of the extracted data is presented in online Table S1 (see Supplementary file 1).

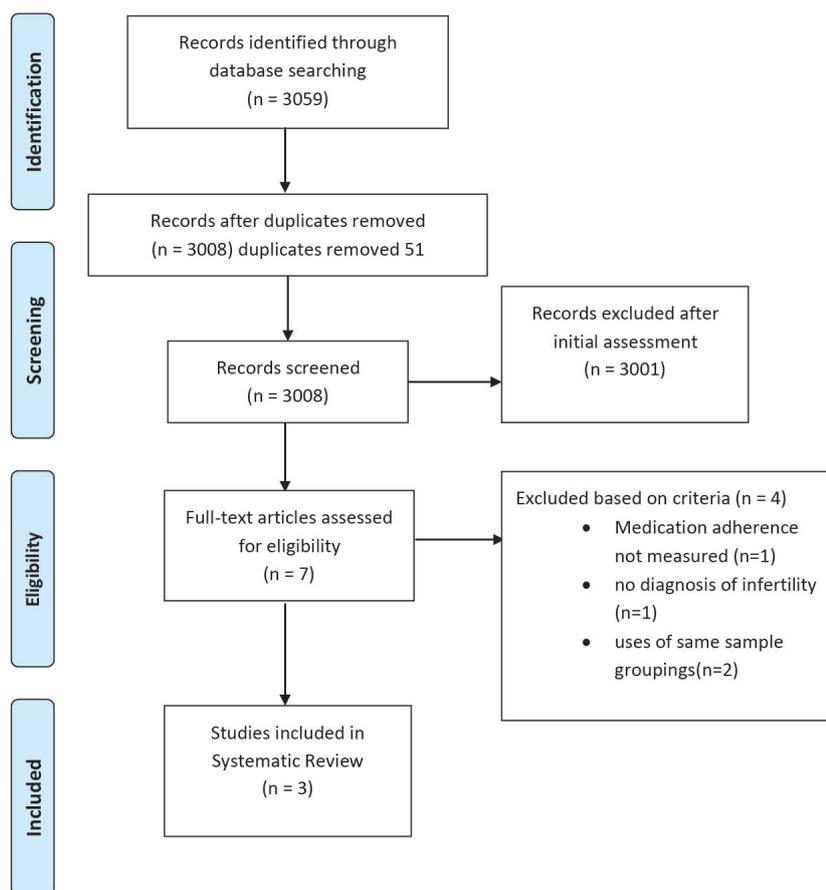


Figure 1. PRISMA Flow Diagram.

Quality Assessment

Critical appraisal was assessed by 2 independent reviewers (DM and CR) using the Downs and Black's (1998) checklist for evaluating the methodological quality of randomized and non-randomized studies and the guidelines of von Elm et al (35) as STrengthening the Reporting of OBServational studies in Epidemiology (STROBE). The STROBE guidelines were used to assess the quality of one study (36) since the Downs and Black criteria were not applicable for non-interventional studies. After the discussion, there was complete agreement between both reviewers respecting the quality of the study. The Downs and Black quality checklist contained 26 items spread across five subscales including reporting (9 items), external validity (3 items), bias (7 items), confounding (6 items), and power (1 item). Items were individually scored by a maximum total score of 32 indicating the highest quality. According to Downs and Black, this tool demonstrated a 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). Additionally, STROBE guidelines were designed as criteria for reporting the observational studies; however, these guidelines were used to assess the methodological rigor of published studies (38). Quality reporting of the

individual studies included in this review is provided in online Table S2 (Supplementary file 1) and Table 1.

Results

Five studies, published during 1990-2011, met the inclusion criteria. However, 2 of these studies were excluded since the remaining 3 studies, conducted by the same authors (39-41), revealed strong similarities of sample characteristics (e.g., age, years of infertility, study location, intervention, and authors), raising suspicion of possible analysis of the same sample. Therefore, only the results of the most recent study of these 3 articles (41) were used in this review analysis in order to ensure the validity of study findings. The 2 earlier studies (39,40) are shaded in online Table S1 and are not included as individual study contributors in the analysis.

Characteristics of Study Participants

The total sample size included 777 participants. Individual study sample sizes ranged from 30 to 626 cases with mean ages ranging between 28 and 30 years. Only one study reported the participant race/ethnicity with the majority (68%) being of Caucasian ancestry (42). In addition, mean body mass index (BMI) ranged from 24.0 to 36.6 kg/m² (36,42). Further, the length of time attempting to conceive

Table 1. STROBE Quality Assessment

	Item No.	Recommendation	Li et al (2011)
Title and Abstract	1	(a) Indicating the design of the study with a commonly used term in the title or the abstract	Yes
		(b) Providing an informative and balanced summary of what was performed and what was found, in the abstract	Yes
Introduction			
Background/rationale	2	Explaining the scientific background and rationale for the investigation being reported	Yes
Objectives	3	Describing specific objectives including any prespecified hypotheses	No
Methods			
Study design	4	Presenting key elements of the study design early in the paper	Yes
Setting	5	Describing the setting, locations, and relevant dates including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(a) Giving the eligibility criteria and the sources and methods of selection of participants	Yes
Variables	7	Clearly defining all the outcomes, exposures, predictors, potential confounders, and effect modifiers. Giving diagnostic criteria, if applicable	No
Data sources/measurement	8*	Giving sources of data and details of methods of assessment (measurement) for each variable of interest. Describing comparability of assessment methods if there is more than one group	Yes
Bias	9	Describing any efforts to address the potential sources of bias	No
Study size	10	Explaining how the study size was arrived at	No
Quantitative variables	11	Explaining how quantitative variables were handled in the analyses. If applicable, describing which grouping was selected and why	No
		(a) Describing all the statistical methods including those used to control for confounding	Yes
Statistical methods	12	(b) Describing any methods used to examine subgroups and interactions	No
		(c) Explaining how the missing data were addressed	No
		(d) If applicable, describing analytical methods taking into account the sampling strategy	No
		(e) Describing any sensitivity analyses	No
Results			
Participants	13*	(a) Reporting the number of individuals at each stage of study (e.g., number of those potentially eligible, examining the eligibility, confirming the eligible ones and including them in the study, completing follow-up, and analyzing the collected data)	Yes
		(b) Giving reasons for non-participation at each stage	Yes
		(c) Considering the use of a flow diagram	No
Descriptive data	14*	(a) Giving the characteristics of the study participants (e.g., demographic, clinical, and social) and information on exposures and potential confounders	Yes
		(b) Indicating the number of participants with missing data for each variable of interest	No
Outcome data	15*	Reporting the number of outcome events or summary measures	Yes
Main results	16	(a) Providing the unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Making clear which confounders were adjusted for and why they were included	Yes
		(b) Reporting the category boundaries when continuous variables were categorized	No
		(c) If relevant, considering the translating estimates of the relative risk into absolute risk for a meaningful time period	No
Other analyses	17	Reporting other analyses performed (e.g., analyses of subgroups and interactions, and sensitivity analyses)	No
Discussion			
Key results	18	Summarizing the key results with reference to the study objectives	Yes
Limitations	19	Discussing the limitations of the study, taking into account the sources of potential bias or imprecision. Discussing both direction and magnitude of any potential bias	Yes
Interpretation	20	Giving a cautious overall interpretation of the results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalizability	21	Discussing the generalizability (external validity) of the study results	Yes
Other information			
Funding	22	Giving 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

varied from 1 year to more than 4 years (36,41). Finally, most of the participants (n=716) were infertile women with polycystic ovary syndrome (PCOS).

Study Location and Practice Setting

Studies were conducted in reproductive medicine/infertility healthcare settings across the United States (42), Germany (41), and China (36). One study (36) addressed the type of payment for services, reporting that 88.9% of the participants were self-paid. In 2 other studies, 34.4%-55% of women underwent prior infertility treatment while 31.1%-36.8% reported a previous pregnancy (36,42).

Study Purpose and Type

In all the 3 studies, medication adherence was examined as first-line therapy. However, none of the studies assessed adherence associated with IUI or IVF cycles. Of course, 2 of the 3 studies (41,42) shared a common purpose to examine the oral medication adherence while the remaining study (36) evaluated the combination of adherence to oral medication and recommendations for weight loss. Furthermore, one study (36) had a prospective, observational design while the other one (41) was prospective and randomized without a control group. Finally, the remaining study (42) was a randomized controlled trial with medication adherence which was examined retrospectively.

Medication Adherence and Theoretical Framework

Researchers in 2 of the 3 studies measured medication adherence using objective measures including medication event monitoring (41) and pill counts (42). The last study (36) measured medication adherence using a subjective measure (i.e., brief medication questionnaire). Moreover, the mean adherence rates ranged from 26% to 81% (36,42). Finally, there was no reporting on specific types of non-adherence (e.g., initiation, execution, and persistence) and none of the studies used a supporting theoretical framework.

Predictors and Barriers Related to Medication Adherence

In 2 of 3 studies (36,41), the researchers investigated possible factors which contributed to treatment non-adherence. The rate of medication adherence was significantly lower when participants were concerned about its side effects or reported 3 or more side effects instead of one or 2 cases (36,41). Additionally, participants who had a BMI < 23 kg/m² or who considered medical treatment to be convenient, had higher adherence rates (36). Eventually, the more frequent medication dosage per day led to a decrease in the adherence rates (36,41,42).

Discussion

As the first one in its kind, the current systematic review was implemented to evaluate medication adherence among women undergoing infertility treatment. Only

3 studies met the criteria for inclusion in this review. Despite the extensive literature on adherence to lifestyle recommendations in women receiving infertility treatment, interest in studies on medication-taking behaviors has been overlooked (6-10,13). The current review study revealed that the rates of adherence to first-line oral medication have a wide variation (26%-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 who take first-line oral medications fail to have as high stakes, namely, time investment, financial commitment, and medical risks compared to those women who undergo more advanced therapy, which can influence the adherence behaviors. However, this review provided evidence that the rates of oral medication adherence are consistent with general adherence rates in the literature which average 50%.

One of the 3 studies in this review addressed a lifestyle factor combined with medication adherence behavior. Li et al examined treatment adherence to oral medications and weight loss recommendations within a subpopulation of infertile and obese women with PCOS (36). Obesity is a lifestyle management factor known to reduce infertility treatment success. In addition, the findings of this review indicated that women who were not obese demonstrate better oral medication adherence (19,43,44). Thus, obese women may be at a higher risk for multiple non-adherence behaviors (45). Further, the results of a recent study demonstrated that 40% of the women seeking infertility treatment actively engage in at least four unfavorable lifestyle-related behaviors which can negatively influence the reproductive outcomes (46). The present novel systematic review provided groundbreaking evidence that behaviors associated with adherence to oral infertility medication are unfavorable. The combination of medication nonadherence and negative lifestyle behaviors present a new conundrum that was not adequately addressed in previous literature for this population.

Furthermore, medication side effects and dosing frequency were observed as potential barriers to adherence (36,41,42). Understanding potential barriers is considered important for optimizing adherence during infertility treatment cycles. As scientists continue to develop strategies for improving innovative reproductive procedures, technology can only be effective if medication protocols are followed. So far, to the best of our knowledge, the relationship between non-adherence behaviors regarding fertility medication and reproductive outcomes (i.e., canceled cycles, clinical pregnancies, and live birth rates) has not been well-documented in the literature. Markle et al found that the failure of women to correctly self-administer the injection medication leads to lower pregnancy rates (33).

Adherence to injection medication was measured in none of the studies from this review although these

medications were problematic for other patient populations such as diabetic patients and those with multiple sclerosis (47,48). 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 the preloaded, multiple-dose, and self-injection pens. Women reported concerns about appropriate self-administering injections (31,32). Some women made medication errors while they failed to report them to the infertility nurse or physician due to either considering the error insignificant or fearing of a negative reaction from the provider (32). Moreover, 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 the medication cost (27). The studies in this review did not examine the women's perspectives on taking fertility medication. However, discrepancies between healthcare providers and clients' perspectives on injection medication-taking behaviors were explored. Although the providers emphasized their concerns about the client's adherence to self-injection medications, they were surprised to find that women were taking incorrect medications, administering incorrect doses, and self-injecting medication incorrectly (25,31).

The infertility healthcare environment, along with the prescribed medication protocols seems to overwhelm the women who undergo infertility treatment. Li et al reported that women who viewed their infertility treatment as convenient indicated higher rates of adherence compared to those who found the treatment inconvenient. Additionally, the burden of treatment was an ongoing problem for this patient population (25,31,32). In fact, the inconvenience of frequent medication injections and the total length of treatment were regarded as central contributors to infertility treatment strain (31). In addition, the clinic environment was reported to worsen the treatment burden and affect the women's decisions to finish the treatment. Factors reported by these women included lack of continuity of care, negative attitudes of the health provider, ineffective communication with clinic staff, and insufficient time for asking their questions (25). A patient-centered care model obtained notable recognition as an indicator of high-quality infertility services (49-51). Thus, understanding the relationship between the quality of care and respective attitudes and behaviors toward medication adherence is of great importance.

Experts have begun an initiative to identify avenues for overcoming the barriers to infertility treatment by improving care for women both nationally and internationally (52). The US health insurance environment was an obstacle for gaining coverage for infertility services (53). Only 15 states passed the laws which required insurers to either cover or offer coverage for infertility diagnosis and treatment although some employers were

provided with infertility coverage in non-mandated states (53). The American Society for Reproductive Medicine released a white paper on the current state of patient access to fertility care in the United States, which outlined several steps to improve access to care including infertility coverage (52). As this initiative moves forward, the urgency to redirect the focus on barriers to medication adherence may become a greater priority.

The literature regarding general medication adherence, the focus was on interventions in order to improve the quality of life, increase life expectancy, and reduce healthcare costs in chronic disease populations (54). In the United States, medication non-adherence was responsible for 125 000 deaths and was estimated to well-exceed \$100 billion in healthcare expenditures annually (55). Further, the average cost per successful pregnancy and birth for women who underwent cycle-based infertility treatment was estimated over \$48 000 (28). Non-adherence to fertility medication is not typically life-threatening although the fertility quality of life is considered a concern (56). Women's perceptions about their experience respecting infertility treatment are associated with the quality of life (51). However, the relationship between fertility quality of life and medication adherence behaviors has not been confirmed.

Strengths and Limitations of the Study

The unprecedented nature of the findings in this systematic review serves as a major strength by offering evidence which oral medication adherence, used as the first-line fertility therapy, can be more problematic than previously assumed by the clinicians and researchers. Two of the 3 studies used randomization into a group assignment, which minimizes the study bias and strengthens the findings. Furthermore, several limitations exist which need to be scrutinized. Studies not published in the English were excluded while those published in other languages may have an effect on the results of the current study. Moreover, the present review included a very small sample size and most study subjects were a subpopulation of infertile women with PCOS, which limits the generalizability of findings; only 3 studies were included for this review after 2 studies were excluded secondary to suspicion of having the same sample grouping. Additionally, the investigated studies were focused only on oral medications during the first-line therapy while not including injection medications nor medication adherence during IUI and IVF treatment cycles. In addition, one study examined medication adherence retrospectively. Although retrospective studies help establish the cause and effect relationships (i.e., contributory factors), the interpretation of the study findings is limited particularly when both selection and recall biases are present. Finally, different instruments were used to measure medication adherence, which could potentially confound the results

and hinder the conclusions of the study.

Implications of the Study

Understanding the patterns of medication-taking is considered important since initiatives are in motion to broaden access to infertility services. Further, reproductive healthcare providers should reinforce the importance of following medication regimens. Furthermore, validating medication adherence in research trials including assisted reproductive therapies can better inform, cultivate, and perpetuate stronger innovative discoveries in reproduction science so as to strengthen the clinical practice.

Recommendations for Future Research

Future investigations are needed for exploring the women's patterns of medication adherence during IUI and IVF cycles. Moreover, insights on how healthcare delivery of infertility services (e.g., the degree of patient-centeredness, communication of the healthcare team, and availability of third-party reimbursement) impact medication-taking could reinforce continuity of care and therefore, medication adherence. The impact of infertility insurance coverage on the rates of medication adherence deserves further attention since healthcare costs continue to skyrocket. Additionally, determining whether the adherence rates differ across the regions of mandated infertility insurance coverage can be beneficial. In addition, the relationship between motivation to conceive and the likelihood of adherence is considered important if the theory-driven interventions are deemed necessary. Further, investigating how the quality of life and environmental factors influence medication adherence is of great significance, particularly when family support and treatment demands (e.g., psychological stress and anxiety, time off work for appointments, and treatment costs) can affect the decisions regarding the continuation of the services. Eventually, the standardization of medication adherence instruments is needed in future infertility research.

Conclusions

In general, the study findings confirm that the research regarding fertility medication adherence remains scarce. Accordingly, further research is timely and compelling. The state of the science on fertility medications is still underdeveloped when compared to general medication adherence research. Aligning medication-taking behaviors with reproductive outcomes (i.e., canceled cycles, clinical pregnancies, and live birth rates) during IUI and IVF cycles in future studies can help determine if the tailored interventions are involved. Furthermore, the rates of oral medication adherence are suboptimal when applied alone as the first-line therapy. Therefore, further investigation is required respecting medication-taking behaviors involving injection medications and controlled ovarian

hyperstimulation cycles associated with IUI and IVF cycles to reinforce the clinical practice. A more extensive exploration into such uncharted territory answers the call of scientific inquiry through fostering innovation and versatility in order to advance human reproduction science.

Conflict of Interests

None declared.

Ethical Issues

Not applicable.

Supplementary Data

Supplementary file 1 contains Tables S1 and S2.

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