Anne Burnett Marion School of Medicine at TCU
Final Prospectus / Thesis

Evaluation of Exogenous Estrogen on IUI Success Rates

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Abstract

Background, Significance, and Rationale:
Patients are often deterred from *in vitro* fertilization (IVF) for contraception assistance due to the cost and turn towards intrauterine insemination (IUI) before attempting IVF. However, for patients under the age of 35, IUI success rates are lower compared to IVF. It is hypothesized that this may be partly due to too thin of an endometrium. Data has demonstrated that a thin endometrial lining, defined as less than 7 mm, has less favorable outcomes in fertility treatments, especially with IVF. The effects of estrogen supplementation on pregnancy outcomes in relation to thin endometrial thickness have not been as thoroughly evaluated in IUI cycles. Additionally, the common practice of rescuing the endometrium with exogenous estrogen has not been adequately studied.

Research Question:
The research question that drove our research was the following: What effect does estrogen supplementation during the ovulation cycle have on pregnancy outcomes compared to patients not receiving estrogen supplementation in women younger than 35 years of age and women aged 35-39 years who desired to conceive via IUI? By determining the effects of exogenous estrogen supplementation on pregnancy success rates, the utility of IUI may be increased as success rates may improve. This would further improve clinical pregnancy success rates for patients without cost acting as a significant burden.

Materials and Methods:
200 patients who underwent IUI between January 19 and September 22 were randomly selected from two categories: patients who utilized estrogen supplementation and controls (ie. no supplementation). Inclusion criteria included normal semen analysis (SA), two patent fallopian tubes, and patients under the age of 40 (stratified into <35 & 35-39). Exclusion criteria include male factor, defined as less than or equal to 5 million motile sperm, BMI greater than 35, smokers, and diminished ovarian reserve (DOR) defined by an anti-Mullerian hormone (AMH) level less than 1. Successful pregnancy was defined as a heartbeat detected (via vaginal ultrasound) at 6.5-7 weeks. For the experimental group, Estrace 2 mg was added (twice per day orally or once per day vaginally) at the initial ultrasound to start the fertility medications or at the follow up ultrasound during the treatment cycle to continue until a heartbeat was detected or a negative pregnancy test resulted. After assessing the normality of distribution of our data, we analyzed the data using an unpaired, two-sample t-test to determine whether estrogen supplementation improved the pregnancy rate associated with IUI.

Results, Conclusions, and Impact:
While we initially anticipated that administering estrogen during an IUI cycle when the endometrium was considered thin would improve clinical pregnancy rates, this research surprisingly found that pregnancy rates were not impacted by exogenous estrogen.

We understand that this is just one study and that we are limited by a small sample size. However, given the results of this research, it may be appropriate to discontinue the use of exogenous estrogen in this patient population. Continuing to utilize this treatment without success may prove fruitless and cost inefficient. This study should prompt additional research with greater sample sizes to further enhance the value of our findings, and if similar findings our discovered, standards should be updated to refrain from utilizing supplemental estrogen with the aspirations of improving clinical pregnancy rates from IUI.

Introduction, Significance, and Rationale

Introduction

As more individuals and couples experiencing infertility turn to intrauterine insemination (IUI), further research is being conducted to evaluate its success, especially in comparison to in vitro fertilization (IVF). A recent UK study listed IUI as a more cost-effective option that delivers similar success rates with lower risks of complications compared to IVF[1].

In 2015, an estimated 48.5 million couples experienced infertility worldwide and within the United States alone, between 1987 and 2015, 1 million babies were conceived through in vitro fertilization (IVF) or other assisted reproductive technologies (ARF) like intrauterine insemination[2,3]. While this may seem like a dramatic number, it's important to consider the challenges associated with infertility treatment. Multiple treatment cycles are often required to conceive with ARFs and these success rates depend on a multitude of factors including age, hormonal disorders, environmental and lifestyle factors, and obesity.

Significance

While there is a wealth of information and data regarding IVF, information regarding the efficacy of IUI is relatively limited. It is well known that IUI is a more cost-effective option for conception, but it is also believed that IVF carries a significantly higher pregnancy and birth success rate[4]. If we as researchers can raise the success rates of IUI to a rate similar to IVF, IUI could raise in ranks and potentially become the gold standard for infertility treatment worldwide. In determining how IUI success rates can improve, we examined current research and data available that could be implemented. As it stands, the current literature details the beneficial effects of supplemental exogenous substances like gonadotropins, clomiphene citrate, and letrozole during IVF and IUI on pregnancy success rates[5]. While exploring the idea of exogenous supplementation, we considered how estrogen supplementation might improve IUI success rates. Chen et. al found significantly higher rates of success in patients undergoing IVF treatment with extended administration of exogenous estrogen[6]. While this proves helpful in rescuing the endometrium to attain success, similar studies have not been conducted in relation to IUI. Demonstrating the positive impact of exogenous estrogen supplementation during an IUI cycle on pregnancy success rates would allow IUI to be used widely and more frequently as a cost-effective alternative to IVF. This would broaden the reach that IUI could have on couples seeking infertility treatment. Thus, we believe further research must be conducted to determine the profertility effect of exogenous estrogen supplementation during IUI.

Rationale

The reason we decided to supplement IUI treatment with exogenous estrogen was to increase conception rates by increasing endometrial thickness. This study is timely, appropriate, and

necessary, given that IVF cycles costs significantly more than IUI[7]. Many researchers worldwide even recommend IUI as a first-choice treatment for infertility and our research could further support this statement by increasing the success rates[8]. For this retrospective data analysis, we utilized a private patient database that included information from 2013-2021. Given that similar studies have been conducted regarding IVF, we believed it would be feasible for us to replicate such studies in relation to IUI[6].

Materials and Methods

General Study Details and Resources

The data from which we are drawing conclusions was obtained from a total of 157 patient files at the Fort Worth Fertility clinic in Fort Worth, Texas after excluding patients due to various criteria. Fort Worth Fertility utilizes paper charts as the main method of storing health records.

Unique Identifier	Age (<40)	BMI (<36)	AMH (>1)	Post Wash #motile sperm (min. 5 mil.)	Follicle #	Success	Cycle #	Time of Supplementation	Route of Estrace admin.	Thickness of endometrium before supplementation	Thickness of endometrium after supplementation
001	29	31	1.74	27.5	18, 23	No	1	Midcycle	Oral	4	6.8
002	34	29	3.26	14.8	16, 16, 18	Yes	2	Start	Oral	3.7	7

Table 1 Data Collection Chart Example

To determine the impact of exogenous estrogen on IUI success rates, a shared, deidentified Google Sheets (Table 1) was created and used to document the retrospective data from all the paper charts. All data was deidentified and a conversion chart (Table 2) was created for study reference, which was stored in a secure and locked room within the clinic. This conversion chart listed the subject names matched with a unique identifier number. The unique identifiers were inputted into the Google Sheet, rather than the subject's name, to ensure privacy. We did not encounter any ethical concerns or harm to any patient affiliated with Fort Worth Fertility. This is because our study was a retrospective data analysis, and the privacy of all subjects was maintained.

Patient Name	**Unique Identifier**
Jane Doe	001
Mary Major	002

Table 2 Example Conversion Chart

Subject Identification

Study participants were selected randomly and reverse-chronologically from the years 2019-2022 from two categories: patients who utilized estrogen supplementation with Estradiol (known as Estrace) during the IUI process prior to ovulation induction as well as a control group of patients who did not utilize supplementation (Group A: 2mg dose vaginally or orally daily until a heartbeat was detected; Group B: non-treatment controls). Patients that had a history of a thin endometrium (defined as <7mm) measured by transvaginal ultrasound were given Estrace. The medications that were used during the treatment were either oral (clomiphene citrate or letrozole) or injectable medications (follicular stimulating hormones).

A total of 157 patients were included in the analysis. 57 patients who underwent IUI with estrogen supplementation were compared against 100 controls. Endometrial thickness before and after Estrace supplementation as well as cycle outcomes were recorded.

Our subject population included patients aged 18-40 years old who have pursued IUI as a patient of Dr. Robert Kaufmann. Inclusion criteria included normal semen analysis (SA) and two patent fallopian tubes. Exclusion criteria included male factor, defined as less than or equal to 5 million motile sperm, BMI greater than 35, smokers, and diminished ovarian reserve (DOR) defined by an anti-Mullerian hormone (AMH) level less than 1.

Additional Subject Stratification

Subjects were further divided into one of two categories within their respective primary group based on age range: younger than age 35 and between 35 and 39 years old. All relevant subject data was recorded in the Google Sheets database with a unique identifier number in order to prevent a breach of confidentiality.

Retrospective Study

Data pertaining to subjects who met the study inclusion criteria was inputted into the Google Sheets database for retrospective analysis. Statistical analysis was performed with the help of a statistician.

Power, Sample Size, and Statistical Analysis

After assessing the normality of distribution of our data, we utilized a two-sample t-test, comparing patients who utilized estrogen supplementation with patients who did not to determine whether exogenous estrogen improved the pregnancy rate associated with IUI. In order to achieve a statistical power of 80% accuracy with an alpha of 0.05 for a two-sample t-test, a minimum of 64 patients was required for each of the two groups. While our aim was to obtain 200 patient charts for each group to ensure this power is achieved, we fell short in the experimental group at 57 patients.

Potential Complications

It is not believed that any complications of this study occurred. However, we had strategies in place in case complications were to arise. We anticipate that if any, they would be related to our inclusion and exclusion criteria. For example, once we inputted all the data into the Google Sheets, if we decided to add a category that required us to go back and pull all charts and amend the information or that would render already-inputted data ineffective, it would require additional charts to be pulled and inputted. To account for this, we added all categories that may have any relevance at all at the start of the study, even if at the beginning of the study they appeared insignificant. These categories included Time of Supplementation and Route of Supplementation. In the future, we may utilize these categories to draw additional conclusions.

Results

A total of 157 patients were included in the analysis. 57 patients who underwent IUI with estrogen supplementation were compared against 100 controls. There were 11 successful pregnancies in the estrogen supplementation group and 16 successful pregnancies in the control group. There was no statistical difference in pregnancy rates between groups (P = 0.4). There was also no difference in pregnancy rates with respect to age (P = 0.8) or endometrial thickness (P = 0.4). There was a higher AMH (P = 0.04) and number of motile sperm (P = 0.03) in the pregnancy groups.

The results of this research project were presented at the American Society for Reproductive Medicine 2022 Conference in Anaheim, California. Our abstract was subsequently published in Fertility & Sterility.

Discussion and Innovation

If the hypothesis for this study was supported by the data collected and the retrospective analysis, it would suggest that pregnancy success rates in patients undergoing intrauterine insemination are positively impacted by exogenous estrogen administration. Given that our study did not demonstrate support of our hypothesis, it may be reasonable to consider halting the practice of exogenous estrogen with IUI. However, taking into consideration our small sample size and the fact that we did not meet our minimum goal of 64 patients in the experimental group, thus impacting the power of the study, we cannot say with certainty that there the exogenous estrogen had no benefit. Further studies with larger sample sizes must be conducted.

An estimated 186 million people globally are impacted by infertility[9] and with the costly price tag associated with *in vitro* fertilization, improved efficacy of intrauterine insemination can provide individuals and couples wishing to conceive with better options than what is currently available. While IUI can aid these individuals at a low cost, evidence demonstrates that IVF has greater success rates with pregnancy. Under the age of 35, IVF has been found to be 41% more effective than IUI and 30% more effective in 35–37-year-old patients[10]. The stress accompanying an infertility diagnosis is evident and often has negative implications on couples who eventually remain unable to conceive. Additionally, for the patient receiving treatment and being affected by assisted reproductive technology, there are medication side effects, financial stressors, and often disappointment associated with each attempt. Our hopes are that a definitive aid in these treatments may reduce attempts individuals and couples must undergo

in order to achieve pregnancy, and decrease costs, medication side effects, and the psychological toll these efforts have on patients wanting to conceive.

If further, subsequent studies with adequate power similarly disprove the notion that exogenous estrogen increases endometrial thickness and thus, improves clinical pregnancy rates, it would provide evidence-based guidelines that physicians can follow in helping their patients achieve pregnancy. As it is, multiple clinics and fertility specialists across the world engage in this practice of administering exogenous estrogen with the hopes of improving pregnancy success rates with IUI. However, if this practice is shown to be ineffective, it can help create more realistic expectations for both patients and providers.

This study takes an already known treatment aid proven to help with IVF success rates and applies it to IUI. Thus, we did expect this retrospective analysis to yield positive results which we could have then definitively apply to current treatment protocols, knowing it is backed by evidence. Our suspicion remains that with a larger experimental group sample size, the results may shift in favor of exogenous estrogen supplementation.

Future Directions

It would be to society's benefit to conduct a large-scale retrospective analysis inclusive of various clinics from across the country following the methods of this study. Having a larger sample size and a larger representation of the population would allow us to draw more accurate conclusions regarding the efficacy of exogenous estrogen supplementation on IUI success rates. Of course, this may not be feasible. As such, it would be productive to continue to collect data on patients who undergo IUI at this specific Fort Worth Fertility clinic so that we can improve the power and expand upon this current study.

Additionally, to strengthen the value of this study, we could evaluate the birthing outcomes of each of the study subjects to determine aspects such as which patients carried to term, which may have miscarried past our "success" time frame of 5-6 weeks, etc.

Subsequent studies could also pivot slightly and evaluate varying doses of Estrace to determine effects on endometrial thickness and clinical pregnancy success rates as well as further delve into the routes of administration of Estrace, looking at the difference in success between oral and vaginal administration.

Conclusion

Overall, this was a very important research question and study reflecting on the efficacy of exogenous estrogen in patients undergoing IUI to achieve a clinical pregnancy. While we had hoped to collect a larger data set and for our results to support our hypothesis stating exogenous estrogen is effective in increasing the success of IUI, we still garnered helpful data. This topic in particular is one that lacks research and even obtaining results against our hypothesis can help us make more evidence-based decisions with patients and hopefully reduce costs of infertility treatment.

Compliance

This study received IRB approval by the Texas Christian University Institutional Review Board. Our study was considered minimal risk, and thus, approved through the expedited process on April 16, 2021 (2021-55). This research study did not require any consideration or approval from IACUC. All researchers affiliated with this study have completed the required CITI trainings.

Resources

This research study was conducted under the supervision and guidance of my mentor, Dr. Robert Kaufmann, who is a Reproductive Endocrinology and Infertility physician in Fort Worth, Texas. The personal laptops of Dr. Kaufmann, myself, and a TCU undergraduate student, Mackenzie Kahrhoff, were used to access a secure, deidentified Google Sheet for data collection, storage, and analysis. All data collection occurred within Dr. Kaufmann's Fort Worth Fertility clinic at 1800 Mistletoe Blvd, Fort Worth, Texas, 76104.

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