2019

The Effectiveness of Two Types of Adjunct Acupuncture Exposures on In Vitro Fertilization Outcomes

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Walden University
2019

Abstract

The Effectiveness of Two Types of Adjunct Acupuncture Exposures on In Vitro

Fertilization Outcomes

by

Lindsey Vacovsky

M.P.H, Walden University, 2010

BS, Lycoming College, 2007

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

Walden University

May 2019

Abstract

One out of every 8 couples experiences infertility. Few publications exist examining the association between the addition of adjunctive therapies when applied to the in vitro fertilization (IVF) procedure and pregnancy outcome. The purpose of this study was to compare the effectiveness of 2 types of adjunct acupuncture exposures on IVF outcomes by applying the concept of the epidemiology triad. The association between the type of adjunct acupuncture exposure received (the independent variable) and pregnancy (the outcome) was determined via binary logistic regression using SPSS software. Medical records of women having received the IVF procedure along with adjunct acupuncture were eligible for analysis. A total of 444 qualifying patient records were collected from participating acupuncture clinics. Analysis of the data showed there was no significant difference in pregnancy outcomes between the two types of adjunct acupuncture reviewed. However, an increase in pregnancy outcomes was noted in the adjunct acupuncture groups when compared with pregnancy outcomes in IVF protocols without the addition of adjunct acupuncture. Additionally, there was no significant difference between pregnancy outcomes when accounting for various race or age groups. This study has implications for positive social change in the form of both providing data to women undergoing the IVF procedure to allow for more informed decision making and ultimately with hopes of improving the odds of success to the nearly 165,000 IVF procedures undergone in America each year.

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Dedication

To the 1 in 8. May you each achieve the success you so desire. You are valued and have been heard.

To my children, I loved you before you were born. Never settle and be the change you wish to see.

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Chapter 1: Introduction to the Study

Introduction

The global health community has recognized infertility as problem that affects

men, women, and couples (Chandra, Copen, & Stephen, 2014). Though the total number

of infertility cases reported has remained stable for the past 40 years, variations by

subgroup, including age, ethnicity, and socioeconomic status remain present (Chandra et

al., 2014). Many efforts have been made to improve maternal and child healthcare;

however, the field of infertility has been neglected in these efforts (Mascarenhas,

Flaxman, Boerma, Vanderpoel, & Stevens, 2012).

Although fertility specialists have offered patients various medications and/or

medical procedures to help increase pregnancy rates, the success of the more invasive

procedures, which are most often reserved for the more difficult cases, remains relatively

low (Malik, 2015; Dieterle, Ying, Hatzmann, & Neuer, 2006). According to Zheng,

Zhang, Wu, & Zhang (2014), however, "The majority of IVF cycles do not result in

pregnancy" (p. 2.). Few publications exist examining the association between the addition

of adjunctive therapies when applied to the in vitro fertilization (IVF) procedure and

pregnancy outcome. More specifically, there are limited studies that focus on a

comparison of various adjunct acupuncture treatments options when applied during the

IVF cycle. Those limited studies then, have weakness and often include a placebo group

whereby either a needle is inserted at an ineffective depth or a sham needle is used in its

place (Hawkins, Rossi, Correia, Lipskind, Hornstein, & Missmer, 2014). The placebo

effect has been well studied and documented making the conclusions of these adjunctive

therapy studies difficult to apply in the clinical setting (Hullender Rubin, Opsahl, Wiemer, Mist, & Caughey, 2015). Although some adjunct acupuncture studies exist, there are few that compare efficacy of various acupuncture protocols. An updated study without the use of a placebo arm and with variable acupuncture exposures was needed to better assess pregnancy outcomes in cases where adjunctive acupuncture therapy was applied to the IVF procedure (Meldrum, Fisher, Butts, Su, & Sammel, 2013). Determining which adjunct acupuncture therapy treatment, if any, was an effective method to increase pregnancy outcome for women undergoing the IVF procedure was an important step in the improvement in fertility treatment. If proven helpful, this added step may be offered during the more than 165,000 IVF procedures undergone in America each year (Christensen, 2014; Doucleff, 2014).

In this chapter I provide some basic background information related to the study topic and articulate the problem statement, research questions, and hypotheses. I explain the nature of the study and the conceptual framework that best defines the study. I also present assumptions, limitations, and delimitations of the design of study along with the rationale as to why this study is important.

Background

The National Infertility Association, known as RESOLVE, reports 1 out of every 8 couples experience infertility (RESOLVE: The National Infertility Association, 2015). This is a similar rate to those experiencing infertility in other developed countries (Bushnik, Cook, Hughes, & Tough, 2012). Approximately, 6% to 11% of women in the United States are affected by infertility (Martinez, Daniels, and Chandra, 2012). The most

common etiologies for female specific infertility are related to blocked fallopian tubes, endometriosis, elevated levels of follicle stimulating hormone (which represents a possible decrease in a woman's ovarian function), and polycystic ovarian syndrome (Rice, Patterson, Wakefield, Reed, Breder, Wurn, King, & Wurn, 2015). Female infertility however, is not limited to those etiologies listed above. In less frequent cases, although still prevalent, women may experience premature ovarian failure or be diagnosed with "unexplained infertility," which represents a classification of the disease in which no cause can be identified (Rice et al., 2015).

Nearly half of all couples shown to have an infertility diagnosis have a partner with male factor infertility (Agarwal, Mulgund, Hamada, & Chyatte, 2015; Shakkebaek, Giwercman, & Kretser, 1994). Approximately 10 to 15% of these male infertility cases can be attributed to genetic causes including chromosomal abnormalities and single-gene mutations. A large proportion of male infertility, however, does not have a clear diagnosis and these cases are then recorded as idiopathic or unexplained infertility (Pizzol, Ferlin, Garolla, Lenzi, Betoldo, & Foresta, 2014).

According to data from the National Survey of Family Growth, the percentage of women aged 15–44 who had ever used infertility services increased from 9% in 1982 to 12% in 2006–2010 (U.S. Department of Health and Human Services, 2005). Chandra et al. (2014) further argued that while reported fertility has remained relatively stable for the past 40 years, variations by subgroup including age, ethnicity, and socioeconomic status remain present. RESOLVE: The National Infertility Association (2015) explained infertility doesn't have a preference on race, gender, or socioeconomic status. Although

the global health community has made improvements in maternal and child health, infertility has been neglected in these efforts (Mascarenhas et al., 2012).

Various treatments and preventative measures are in practice to preserve fertility, prevent infertility, and treat those diagnosed with infertility. Acupuncture is one such treatment that has been applied with the intent to treat fertility issues (Dieterle et al., 2009; Qu, Zhang, Chen, Wang, Pan, Zhu, Ma, Huang, Ye, Sun, Zheng, Zhang, Xu, Xing, & Huang, 2014). Various studies considered how acupuncture can be applied to the IVF procedure, but analysis of such studies showed lack of a standard acupuncture protocol being performed (Meldrum Fisher, Butts, Su, & Sammel, 2013; Zheng et al., 2014;). Other studies, as identified in a meta-analysis conducted by Manheimer Zhang, Udoff, Haramati, Langenber, Berman, and Bouter (2008) lacked the appropriate number of participants. A lack of consideration of confounding factors was identified in another retrospective chart review (Hullender Rubin, Opsahl, Taylor-Swanson, & Ackerman, 2013). Others argued a fundamental design flaw is present in placebo-controlled acupuncture studies because even the "controls" are likely to have physiological effects (Hullender Rubin et al., 2015).

Presently, there is a gap in the literature that addresses pregnancy outcomes following adjunct acupuncture exposure. Additional research is needed to control for the type of acupuncture that is applied, the timing of treatments, as well as, take into consideration confounding variables. Considerations need to be in place to limit the possibility of the placebo effect influencing the data and thereby influencing the conclusions that are drawn.

Problem Statement

Nearly 1 out of every 8 couples experience infertility (RESOLVE: The National Infertility Association, 2015). Approximately 12% of the United States' population of women have undergone the IVF procedure in an attempt to achieve a successful pregnancy (RESOLVE: The National Infertility Association, 2015). Identification of effective adjunctive therapies to increase the success of IVF could decrease the number of attempts necessary to achieve pregnancy and thereby increase the number of women who would find success in the IVF procedure. Options for women who undergo several IVF cycles without success remain unsatisfactory (Dieterle et al., 2006; Fogarty & Smith, 2016; Shen, Wu, Shu, Zhao, & Gao, 2015).

Acupuncture has been used to treat infertility symptoms such as ovulatory disorders, male infertility, stress, and anxiety with studies showing various health benefits of its use (Dieterle et al., 2009; Jo et al., 2015; Johansson et al., 2013; Qu et al., 2014). Given the marked success of acupuncture to treat infertility related symptoms, the next logical step was to study acupuncture as an adjunct to the IVF procedure. Presently, there are conflicting articles as to the efficacy of various applications of adjunct acupuncture therapy when applied during the IVF cycle (Fogarty & Smith, 2016; Paulus, Zhang, Strehler, El-Danasouri, & Sterzik, 2002; Zheng et al., 2012). Some argued the necessity of acupuncture treatments on the day of embryo transfer as the only way to significantly increase pregnancy outcomes (42.5% vs. 26.3% of patients without acupuncture; Dieterle et al., 2006; Paulus et al., 2002; Westergaard, Mao, Krogslund, Sandrini, Lenz, & Grinsted, 2006), while others argued multiple treatments of acupuncture are needed to

treat the body as a whole before a significant increase in pregnancy outcomes following IVF are shown (di Villahermosa, dos Santos, Nogueira, Vilarino, & Barbosa, 2013; Stener-Victorin, Waldenstrom, Andersson, & Wikland, 1996; Zheng et al., 2012).

Much of the literature compared one form of acupuncture to placebo and acknowledged the weakness of such designs (Hullender Rubin et al., 2015; Meldrum et al., 2013; & So, Ng, Wong, Lau, Yeung, & Ho, 2009). Some data showed that both adjunct acupuncture and placebo acupuncture increased pregnancy rates when compared with the IVF procedure alone (Shen et al., 2015; So et al., 2009). Research comparing the two different theories of acupuncture administration as an adjunct to IVF treatment is largely absent from the research literature. That is, the literature does not clearly identify if one form of adjunct acupuncture results in more pregnancies than the other.

Presently, no research studies have been found that apply either race or age to the success of the IVF after the addition of adjunct therapy has been applied. In this research I aimed to identify if an association between increased successes of IVF procedures was present with the addition of the various forms of adjunct therapy. If present, this increased success could have possibly shown a reduction of some of the disproportionate success rates among different age or race groups. Identifying if a specific protocol of adjunctive acupuncture would increase pregnancy outcome may offer additional information that would help women to make better choices when it comes to their fertility and the aid they seek when attempting to become pregnant after an infertility diagnosis.

Purpose of the Study

The current success rates following IVF are unsatisfactory (Dieterle et al., 2006; Fogarty & Smith, 2016; Shen et al., 2015) as nearly 83% of IVF cycles do not result in a live birth (Wang, Macaldowie, Hayward, Chambers, & Sullivan, 2009). The purpose of this study was to evaluate the efficacy of different adjunctive acupuncture therapy exposures when applied during the IVF cycle. The approach used was a quantitative study design comparing IVF outcomes (pregnancy yes/no) between women who had received acupuncture therapy both pre- and post-embryo transfer for a total of two exposures, one treatment pre- and one treatment post-embryo transfer and women who received IVF with a series of acupuncture treatments (five or more treatments up to and including embryo transfer) during a single IVF cycle (the referent group). Although general guidelines report the number of acupuncture treatments can vary depending on personal response as well as the condition being treated (California State Oriental Medical Association, n.d.; NorthStar Natural Medicine, n.d.; Live Oak Acupuncture & Wellness Center, 2017). Middleton (2017), a certified acupuncturist, explained that most often between four and eight treatments are necessary to see results. For the purposes of this project a minimum of five acupuncture treatments was required to be eligible for one group of the retrospective study. To meet qualifications to be considered for the exposed group, the medical record must have shown that the woman received acupuncture pre- and post-embryo transfer only (a total of two treatments within 72 hours of transfer). I collected the data from existing medical records at the participating acupuncture clinics. The purpose of this study was to better understand if one form of adjunctive acupuncture

was more likely to result in a positive pregnancy result following the IVF cycle compared with another form of standard acupuncture (the referent group).

Research Questions and Hypothesis

RQ1: Is receiving acupuncture pre- and post-embryo transfer, associated with pregnancy?

$H_0 1$: Receiving acupuncture pre- and post-embryo transfer is not associated with pregnancy.

$H_a 1$: Receiving acupuncture pre- and post-embryo transfer is associated with pregnancy.

RQ2: Is receiving acupuncture pre- and post-embryo transfer associated with pregnancy when controlling for age of women?

$H_0 2$: Receiving acupuncture pre- and post-embryo transfer is not associated with pregnancy when controlling for age of women.

$H_a 2$: Receiving acupuncture pre- and post-embryo transfer is associated with pregnancy when controlling for age of women.

RQ3: Is receiving acupuncture pre- and post-embryo transfer associated with pregnancy when controlling for race of women?

$H_0 2$: Receiving acupuncture pre- and post-embryo transfer is not associated with pregnancy when controlling for race of women.

$H_a 3$: Receiving acupuncture pre- and post-embryo transfer, is associated with pregnancy when controlling for race of women.

The additional variables of race and age were collected via patient medical records found in the participating acupuncture clinics. Analysis of the data included a binary logistic regression analysis for all individual research questions.

Conceptual Framework

There are no well-known, well-documented theoretical frameworks for adding therapies in a clinical setting to increase pregnancy outcome following assisted reproductive technologies (ART). However, I employed the epidemiologic triad as the theoretical framework for this study. Although originally implemented to study the cause of infectious diseases, the epidemiologic triad has been applied to noninfectious disease as well (Miller, 2002). The epidemiologic triad is a theoretical concept that applies three factors. The host, agent, and environment all interact with one another in various ways and therefore the outcomes are that of various states of health. The host factor, in this instance, was either age or race. As a general guidance, the agent is defined as the factor that must be present for the disease to occur (Virtual Campus of Public Health, n.d.). In the case of this protocol, the agent was defined as the IVF procedure. For a patient case to have been eligible for evaluation, a participant must have undergone the complete IVF procedure. That is, the patient must have had at least one embryo transferred back into the uterus and been followed through to pregnancy testing. Any cycle in which embryo(s) were not transferred back into the uterus did not qualify. The frequency of the addition of adjunctive acupuncture therapy is what I studied (the dependent variable), and therefore this therapy represented the various environments as part of the epidemiologic triad model. The environment was defined as all that is external to the host. These factors often

include biological factors and socioeconomic factors such as access to care and the type

of care that is received, frequency of adjunctive acupuncture therapy in this case.

Table 1

Table of Constructs for Proposed Research

Construct	Variable	Comment
Host	Age and Race (Categorical)	Both the Age and Race categories for this study was based on the existing demographic data present in the patients' medical record found at the Acupuncture clinic(s)
Agent	IVF (Yes)	Individuals with infertility diagnosis that have undergo IVF. Completing an IVF cycle was a requirement for a patient chart to be eligible for review. Data was collected from Acupuncture clinic(s)
Environment	Frequency of Acupuncture - Pre- and post-embryo transfer only (total of two acupuncture exposures at specified time points) or - Five or more acupuncture treatments at any time point within the cycle up to and including embryo transfer (referent group)	Frequency of acupuncture was collected into one of two groups; either pre- and post-embryo transfer only (total of two acupuncture exposures at specified time points) or a frequency of five or more treatments up to and including embryo transfer (referent group). Data was collected from Acupuncture clinic(s)

Evidence suggested the presence of racial disparities in the success of IVF procedures (Humphries, Chang, Humm, Saklas, Hacker, 2016; McQueen, Schufreider, Lee, Feinberg, Uhler, 2015). Data also supported claims that age is a strong indicator of IVF success (Revelli, Biasoni, Gennarelli, Canosa, Dalmaso, Benedetto, 2016; Shapiro, Daneshmand, Desai, Garner, Aguirre, Hudson, 2016). Presently, there are no research studies that apply either race or age to the success of the IVF after the addition of adjunct therapy has been applied. In this research I aimed find any associations between increased successes of IVF procedures with the addition of the various forms of adjunct therapy thereby eliminating some of the disproportionate success among different age or race groups. A more in-depth discussion of the conceptual model is found in Chapter 2.

Nature of the Study

The conceptual framework that was the basis for the study design was the epidemiologic triad. The study was a quantitative retrospective study. The independent categorical variable was the frequency of adjunctive acupuncture therapy received. The exposed group had received two acupuncture exposures, pre- and post-embryo transfer only and the nonexposed group had received five or more acupuncture treatments completed up to and including embryo transfer during a single IVF cycle (the referent group). The dependent categorical variable was pregnancy (yes or no) by the 9th week following embryo transfer. In addition, I collected selected demographics from the patient charts (age and race) to identify if such adjunct acupuncture exposure results in more pregnancies in a particular category of individual compared with another. If it was available in the medical record, I also collected data on whether previous IVF cycles had

been completed (yes/no) as a confounder. An original randomized controlled trial was not feasible at the time this research study was conducted due to lack of sufficient sponsorship and physician oversight in clinical care. Therefore, this study was completed through a retrospective cohort review. As attempts to balance the individual's Qi is the historical intent of treating with acupuncture (Moy et al., 2011), the referent group for the protocol was defined as women receiving five or more treatments of acupuncture up to and including embryo transfer. The exposed group was defined as women who had some alteration in the standard acupuncture treatment, that is, women who received acupuncture pre- and post-embryo transfer only.

Sources of Data

I pulled a random selection of eligible patient charts from participating acupuncture clinics. To meet eligibility criteria, the patient chart must have had a record of the patient having completed an IVF procedure while undergoing adjunctive acupuncture. The eligible chart must have also stated the frequency of the acupuncture received during the IVF cycle as well as when during the IVF cycle the acupuncture was delivered. Demographic data inclusive of the patients' age and race must also have been recorded and available for review. Finally, the eligible chart must have also included the outcome of the IVF procedure (positive pregnancy or not, as reported by the patient).

Statistical Procedures

G* Power software was used to determine the appropriate sample size with study design equal to a two-tailed study with an alpha of 0.05, power at 0.80%, and an OR value of 1.885, as calculated from existing literature (Hullender Rubin, Opsahl, &

Ackerman, 2012; Hullender Rubin et al., 2015). I performed binary logistic regression with the collected data as both the independent and dependent variable were categorical in nature with only two categories. I conducted modelling using multiple logistic regression to include all variables and to predict the most parsimonious model.

Operational Definitions

It is imperative for the reader to have a clear understanding of the terminology that is used throughout this dissertation document and in the summary of literature reviewed. Concise descriptors of the dependent variable, independent variable, the two covariates, and other descriptors that may help the reader are presented below.

For this research study, the independent variable was defined as the type of adjunctive acupuncture exposure received (exposed or nonexposed). The dependent variable was documentation of a clinical pregnancy via any patient reported method. The covariates considered for this study included race and age. Further clarification of these definitions follow.

Adjunct therapy: An additional treatment (also known as adjunctive therapy) that is used together with a primary treatment. The purpose of the adjunct therapy is to supplement/ assist the primary treatment goals (U.S. National Library of Medicine, 2016). For this protocol, the type of adjunctive acupuncture therapy received was considered the adjunct therapy. The exposed group was defined as women receiving a total of two acupuncture treatments, one just before (within 48 hours prior to transfer) and another up to 24 hours following the embryo transfer portion of the IVF procedure. The nonexposed group was defined as women having received a total of five or more

acupuncture treatments being performed during a single IVF cycle up to and including embryo transfer.

Assisted reproductive technologies (ART): All treatments or procedures that include the in vitro handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy. ART does not include artificial (intrauterine insemination) (U.S. Food and Drug Administration, 2016).

Clinical Pregnancy: Evidence of pregnancy by confirmation of fetal heartbeat via ultrasound parameters (ultrasound visualization of a gestational sac, embryonic pole with heartbeat). Clinical pregnancies include ectopic pregnancy. Multiple gestational sacs in one patient are counted as one clinical pregnancy (U.S. Food and Drug Administration, 2016). For this protocol, documentation of a clinical pregnancy was defined as either a documented report of a patients' verbal confirmation of pregnancy to the acupuncture clinic or the acupuncture clinic's documentation of receipt of pregnancy results from another clinic or laboratory.

Embryo: Product of conception from the time of fertilization to the end of the embryonic stage eight weeks after fertilization (U.S. Food and Drug Administration, 2016).

Embryo transfer: Procedure in which the embryo(s) are placed in the uterus or fallopian tube (U.S. Food and Drug Administration, 2016).

In-vitro fertilization (IVF): An ART procedure that involves extracorporeal fertilization (U.S. Food and Drug Administration, 2016).

In-vitro fertilization cycle: Similar to a menstrual cycle; however, during an IVF cycle no ovulation takes place (Genetics & IVF Institute, 2017). For this protocol, one IVF cycle was defined as the time between the first day of a woman's last menstrual period until pregnancy test is administered or the presence of the next menstrual period (whichever is first). A single cycle included time for egg maturation, collection from ovaries, fertilization in lab, and embryo(s) implantation into uterus or time for uterine prep and embryo transfer if frozen embryos were used

Standard of care procedures: Diagnostic and/or treatment process that a physician would use to routinely treat a certain type of patient with any given condition. (MedicineNet.com., n.d.). From a legal standpoint, the standard of care procedure can be defined as how a similarly qualified health care provider would have managed the same patients' care given the same conditions. For this research, the standard care procedure was defined as the IVF procedure without any added patient specific criteria.

Assumptions

The assumptions in this study mostly related to the primary data collection source. The study design was such that a sample of medical charts were pulled. The assumption was that these samples were representative of both the infertility population and of the women who will seek the assistance of IVF while trying to become pregnant.

I also assumed that the medical records of the selected cases were recorded accurately, in their entirety, and without any bias. The cases pulled from the acupuncture clinic involved additional assumptions that similar acupuncture treatments were applied

to each case and that no additional variables were introduced such as herbs or supplements.

General assumptions on all cases (applying to both the exposed and nonexposed groups) were that no genetic concerns for embryo survival were present and that all women received similar medical care and a standardize IVF treatment protocol.

All of these assumptions were necessary in the context of this study because each of these factors may have introduced additional variables and/or confounding factors that may have influenced the pregnancy outcome following the IVF procedure(s). Limitations as a result of the retrospective nature of this study design cannot be corrected as there was no patient interaction and the study design was purely chart review in nature.

Scope and Delimitations

In this study, I focused on pregnancy outcomes following the IVF procedure. I also collected data on which type of adjunctive acupuncture therapy was received (exposed or nonexposed as described in above sections) along with the patients' age and race. I selected the topic as a result of the limited success rates of the current IVF procedures coupled with the increase in their use (Centers for Disease Control and Prevention, 2015). The variables were selected as a result of availability within the existing database structure. The retrospective nature of the study required the use of the previously collected categorical variables (both age and race). As this format is how the data was proved to me as researcher, no further stratification of the data can occur.

The epidemiological triad conceptual framework itself is a delimitation of the research in that three factors limit the makeup of the framework. A more detailed explanation of this framework appears in Chapter 2.

The retrospective data that I used for this research has previously been collected from within the United States and as such, the IVF procedures performed on patients used only approved equipment, techniques, and locations. Similarly, U.S. given standards were placed on the adjunctive acupuncture treatment. The results of the study therefore may not be generalizable to areas of the world with different restrictions or requirements of the same or similar procedures.

Limitations

The research has limitations that were directly related to the retrospective nature of the medical charts used for data collection. The variables available were those that have previously been collected; therefore, there were limited opportunities to seek clarification of variable responses. Retrospective data provides no opportunity to change how the data was collected, that is, a researcher may not have enough information to switch a variable collected categorically to its most detailed form (Hess, 2004). Biases and errors in reporting may have been recorded in the medical records that were selected for review of this study. There is no opportunity to remove or account for these biases and/or errors in the primary data collection process. It was the approach of the research to randomly select charts for review (among those cases identified as having completed the IVF procedure with the addition of adjunctive acupuncture therapy).

The dates in which the procedures were originally performed was also a limitation in that, advancements in techniques and clinic facilities are likely to have been made since the data became available for public use, in this case, the retrospective review. Therefore, pregnancy rates may have changed before analysis and/or publication of findings making the conclusions less applicable under current standards of treatment. Other limitations included the disproportionate use IVF among different age and race categories (Chandra et al., 2014) thereby potentially not allowing for a fair representation of the makeup of the population. The reasons for this disproportionate use of various ART procedures was, at the time of submission of this dissertation, still being studied.

The statistical methods that I used for this quantitative research study can only identify associations. It is important to remember that causation cannot be determined providing further unavoidable limitations to the design. The odds ratio was used in the statistical analysis of data collected.

To address the limitations of this study design, only patient charts from 2012 or later were collected.

Significance

Many studies on acupuncture have shown its benefits to improving a patient's fertility (Jo et al., 2015; Johansson et al., 2013; Dieterle et al., 2009; & Qu et al., 2014). Fewer studies have looked at acupuncture as an adjunct to IVF (Manheimer et al., 2008). Although these studies are informative, the vast majority compared adjunct acupuncture to placebo (Zhang et al., 2015). This information is not useful to a woman who has

decided to receive adjunct acupuncture but is uncertain about which type of treatment might encourage the positive pregnancy result she has seeking.

The number of women usingART is increasing (Christensen, 2014; Doucleff, 2014), and the number of women seeking adjunct therapy to support their efforts in becoming pregnant is also increasing (Zhang et al., 2014). Comparisons among various forms of adjunctive acupuncture when applied to the IVF cycle have gone largely unstudied. This study has important implications for broadening our understanding of the fertility treatments available to us. The findings of this study are useful for the medical community in its efforts to care for the public by addressing the unmet needs of the infertile population seeking medical care in their attempt to have a child.

Providing data that compares the efficacy between two well-studied forms of adjunct therapy during the IVF cycle not only fills a gap in the literature but also may help women be better-informed consumers of the various options of adjunct acupuncture therapy. Interested parties may use the conclusions from this study to reconsider the recommendations or considerations of adjunctive therapies. The benefits associated with this type of policy change has the power to provide the nearly 83% of women who, under the standard protocol, would have an unsuccessful IVF cycle (Wang et al., 2009) the opportunity to experience pregnancy. Inclusion of these services in the standard IVF treatment could potentially reach the 7.4 million women who have sought infertility care (RESOLVE: The National Infertility Association, 2015).

Summary

In this chapter I presented a brief background for the study. I identified the

problem statement clarifying the purpose of the study. I presented clear research

hypotheses along with a short description of the selected conceptual model used in this

study. I also provided an overview of assumptions, limitations, and scope of the study. I

presented a concise explanation as to the significance of the study as well as the

implication for social change in this chapter. I present a detailed review of the current

literature in Chapter 2. This chapter offers a rationale for the methodology of the research

and provides support for the need to continue our understanding and attempts at

improving the success rate of the IVF procedure.

Chapter 2: Literature Review

Introduction

The Practice Committee of the American Society for Reproductive Medicine (2013) defined infertility as the failure to achieve a successful pregnancy after 12 months of timed unprotected intercourse. For women over the age of 35, earlier interventions have become standard of care; therefore, the diagnosis of infertility in this population is defined as the failure to achieve a successful pregnancy after 6 months of timed unprotected intercourse. The global health community has recognized infertility as problem that affects men, women, and couples (Chandra et al., 2014). It is a global multiethnic problem that affects 50-79 million couples worldwide (Boivin, Bunting, Collins, & Nygren, 2007). Chandra et al. (2014) added that while reported fertility has remained relatively stable for the past 40 years, variations by subgroup including age and ethnicity remain present.

Although the global health community has made improvements in maternal and child health, infertility has been neglected in these efforts (Mascarenhas et al., 2012). Fertility specialists have offered patients various medications and/or medical procedures to help increase pregnancy rates; however, the success of the more invasive procedures, which are most often reserved for the more difficult cases, remains relatively low (Dieterle et al., 2006; Lintsen et al., 2007; Malik, 2015; Vahratian, 2008). Wu, Henne, and Propst (2012) argued that the cost of IVF is a burden for many of the patients undergoing fertility treatments. However, there is no guarantee that undergoing such an invasive and expensive procedure will bring about a successful pregnancy, and thus

multiple attempts are often needed (Meldrum et al., 2013). Even within the small number of success stories, racial and age disparities in IVF outcomes remain prevalent (Baker Luke, Brown, Alvero, Frattarelli, Usadi, Grainger, & Armstrong, 2010; Huddleston, Cedars, Sohn, Giudice, & Fujimoto, 2010).

Acupuncture alone has been used to both treat and maintain fertility (Qu et al., 2014; Dieterle et al., 2009). Numerous studies considered how acupuncture can be applied to the IVF procedure but analysis of such studies showed a lack of a standard acupuncture protocol being performed (Zheng et al., 2014; Meldrum et al., 2013). Other studies either lacked an appropriate number of participants (Manheimer et al., 2008), consideration of confounding factors (Hullender Rubin et al., 2013), or had design flaws not accounting for the presence of the placebo effect of acupuncture treatments (Hullender Rubin et al., 2015). Similarly, these studies report success levels for women as a whole and do not make a point to distinguish how the success of the procedure varies among different races. Similar still, few articles attempt to identify specific protocols that would work best within various subsets such varying racial or age groups. In this research I aimed to identify if the group of women's exposure to adjunct acupuncture treatment (pre- and post-embryo transfer) influenced pregnancy outcomes following the IVF procedure. In addition, the research identified if the adjunct acupuncture procedure would lessen the disparities present between the successful outcomes of the IVF procedure among various racial or age categories.

Through this chapter I summarize the literature search strategy, identifying both key words and sources. I provide a description of infertility and what is currently

understood about acupuncture as a fertility aid. I touch upon the disparities present in the success following an IVF procedure. Additionally, I discuss the conceptual framework that the study on which based and conclude with a summary of this chapter and transition to the next.

Literature Search Strategy

I collected the information for this literature review via mining web-based libraries. I reviewed electronic versions of medical journals, databases, websites, and published dissertations. The electronic search engines I uses included Academic Search Premier, Educational Resources Information Center (ERIC), EBSCO, Library Information Science, MEDLINE, Proquest, and PUBMED. I used publishers' databases such as Elsevier, ScienceDirect, and Springer as well. I selected articles from journals such as *American Journal of Obstetrics & Gynecology, BMJ, Evidence-Based Complementary and Alternative Medicine, Fertility and Sterility, Human Reproduction, Reproductive BioMedicine Online, Journal of Advanced Medicine, Journal of Assisted Reproduction and Genetics, Journal of Alternative and Complementary Medicine, Journal of Infertility and Reproductive Biology, Journal of Translational Medicine,* and *PLoS ONE.*

Limitations of the literature search included that parameters were set to publications presented in the English language only, access to full text articles, human subjects, and articles from 2012 to current (as of the time of the literature search). I used the following keywords to further refine the literature search: *Acupuncture, age, infertility, alternative medicine, assisted conception, assisted reproductive technology*

(ART), in vitro fertilization (IVF), IVF outcomes, racial disparities, infertility risk-factors, IVF pregnancy rates, and combinations of these words.

To supplement the article selection, I scheduled daily automatic e-mails to be sent to my e-mail accounts by Google Scholar when the title or subject included *infertility, IVF, in vitro fertilization,* or *acupuncture* in combination with *fertility* and/or *IVF.* A few articles that I used in the completed dissertation fell outside of these parameters such as those listed as secondary sources and found in the reference list of other publication. These referenced articles were the exceptions and may have been selected for further evaluation. In addition, when the quantity of articles on a particular topic was sparse, I allowed for older publication dates to be incorporated into the literature review. I completed an additional literature review that provided supplemental support for the conceptual framework for the study. The observations of this additional review are explained in the section below.

Conceptual Framework

There are no well-known, well-documented theoretical frameworks for adding therapies in a clinical setting to increase pregnancy outcome following ART. However, for the purposes of this research, the epidemiologic triad acted as the framework on which the study was centered. Although originally implemented to study the cause of infectious diseases, the epidemiologic triad has been applied to noninfectious disease as well (Miller, 2002). Some of the more noteworthy studies that applied the epidemiological triad to noncommunicable disease include a study focusing on the health of gamblers and new gambling technology (Peller, LaPlante, & Shaffer, 2008). Traumatic

injuries as a result of earthquakes have also been studied using the epidemiologic triad (Ramirez & Peek-Asa, 2005).

The epidemiologic triad is a theoretical concept that contains three apexes, the host, the agent, and the environment. Each of these parts interact with one another to various degrees and in different combinations resulting in various outcomes. The host factors encompass the demographic characteristics of the individuals being studied. Host factors can include socioeconomic status, age, race, behavioral factors, and so forth (Bhopal, 2002). As a general guidance, the agent is defined as the factor that is capable of causing the disease. However, the presence of the agent is not always needed in order for the disease to occur (Virtual Campus of Public Health, n.d.). An example is that of the relationship of lung cancer and smoking. It is general knowledge that smoking causes lung cancer, but individuals may still develop lung cancer even if they were never smokers. The typical agent factors include bacteria, virus, or other biological agents. They can also be physical factors such as noise, temperature, radiation, and so forth (U.S. Department of Health and Human Services, 2006). The environment factor is defined as all that is external to the host. These environmental factors affect the agent and therefore the opportunity of exposure. Environmental factors can include the climate, insects, sanitation, etc. (Virtual Campus of Public Health, n.d.).

For this dissertation, the three factors were applied as follows:

- The Host: The host factors were those nonmodifiable demographic factors that related directly to the subjects in this study, that is, the age and race of the women who undergo the IVF procedure with the presence of adjunctive

acupuncture therapy. Evidence suggested the presence of racial disparities in the success following IVF procedures (Humphries et al., 2016; McQueen et al., 2015). Data also supported claims that age is a strong indicator of IVF success (Revelli et al. 2016; Shapiro et al. 2016).

- The Agent: The agent factor is most often defined as what can cause the disease. As it applied to this research, the epidemiologic triad was not used for studying a disease but rather an outcome. Therefore, the agent in this situation was the presence of the IVF procedure itself. The details of the agent were captured in a Yes/No manner. For a patient case to be eligible for evaluation, a participant must have undergone the complete IVF procedure. That is, the patient must have had at least one embryo transferred back into the uterus and been followed through to pregnancy testing.

- The Environment: The environmental factor is defined as all that is external to the host. For this research, the environmental factor was the type of adjunct acupuncture treatment exposure. The participants were categorized into two main groupings. The first group, the exposed group, were women who received adjunct acupuncture treatments pre- and post-embryo transfer only (pre- and post-embryo transfer). The second group, or the nonexposed group, were participants who received adjunct acupuncture treatments 5 or more times within an IVF cycle prior to embryo transfer.

To provide a concise summary, the conceptual framework for this study was the epidemiologic triad. When the agent is present (in this study, the IVF procedure), the host

and environment may influence outcomes. Knowledge of the disparities present in the success of IVF procedures among various racial groups and aging women in both environmental scenarios (both forms of adjunct acupuncture studied) may allow for better informed clinical-decision making by both patients and physicians. Understanding these disparities may support treatment modifications improving "the potential for success in certain populations" (Humphries et al., 2016, p..212). In the following sections I provide some background statistics, discuss the disparities in greater detail, and provide information on the types acupuncture used in conjunction with ART.

Study Design

An original randomized controlled trial is not feasible at this time due to lack of sufficient sponsorship and physician oversight in a clinical setting. Therefore, this study was completed through a retrospective cohort review. Although most cohort studies are prospective in nature, the sample size needed to estimate the relative risk of a pregnancy outcome in the infertile population is too large to be feasible (StatsDirect Limited, 2017). Another limitation of a prospective study is the time one must commit to completing the data collection (StatsDirect Limited, 2017). If the research was prospective in nature, collection from a single patient could take more than 14 weeks (from time of first acupuncture treatment to 9 weeks post-embryo transfer). Factoring in this length of time and the number of cases needing collection could expand the data collection for this study into years. El Masri (2014) recommended conducting a less expensive retrospective cohort studies prior to conducting longer, more costly prospective studies. In this study

design, the pregnancy outcomes were collected from existing medical records found at an acupuncture clinic and exposure status must have been reported.

The retrospective cohort study design allowed for calculation of incidence of pregnancy in both adjunct acupuncture groups, exposed and nonexposed groups (LaMorte, 2016). Analysis of the data provided incidence and relative risk of pregnancy the various racial and age groups. Retrospective cohort studies are not without their disadvantages. As with all retrospective studies, the researcher is limited to data sources that are already in existence and therefore, it is possible confounding factors were never collected or recorded (LaMorte, 2016; StatsDirect Limited, 2017). Variables such as embryo quality, number of embryos transferred, and the physical features of the uterine cavity have all been shown to influence the outcome of IVF (So et al., 2009), but given the clinical nature of these variables they may not have been collected and recorded in the acupuncture clinic notes. Additionally, having not been present for the initial data collection, I could not be certain of the accuracy of the archived data (El-Masri, 2014). In this study design, I needed to trust that the pregnancy outcome, age, and race was recorded correctly.

Infertility

Infertility is a disease of the reproductive system (Zegers-Hochschild, Adamson, Mouzon, Ishihara, Mansour, Nygren, Sullivan, & Vanderpoel, 2009). The Practice Committee of the American Society for Reproductive Medicine (2013) defined infertility as the failure to achieve a successful pregnancy after 12 months of timed unprotected intercourse. If the woman is younger than 35, infertility can be diagnosed after six

months of clinically not being able to achieve a pregnancy (Eunice Kennedy Shriver National Institute of Child Health and Human Development, n.d.). RESOLVE: The National Infertility Association (2015) elaborated on this definition explaining failure to establish a clinical pregnancy can be due to an individual impairment or as a result of an impairment with a partner.

Pregnancy is the outcome of many interwoven steps. First a women's body must release an egg from an ovary (this step is called ovulation). Fertilization must then occur as a single sperm joins the egg in the women's reproductive tract. The fertilized egg (egg and sperm combined) must then travel through the women's fallopian tube. Once in the uterus, the fertilized egg must attached (implantation) (Centers for Disease Control and Prevention, 2017). Any reoccurring problem in any one of these steps can cause fertility concerns (World Health Organization, 2017). If a couple or an individual chooses to seek assistance, The Centers for Disease Control and Prevention (2017) recommend seeking out a Reproductive Endocrinologist (RE). REs are credentialed individuals that specialize in managing infertility.

Epidemiology of Infertility

The RESOLVE: National Infertility Association, known as reported 1 out of every 8 couples experience infertility (RESOLVE: The National Infertility Association, 2015). This is a similar rate to those experiencing infertility in other developed countries (Bushnik et al., 2012). Martinez et al. (2012) reported 6% to 11% of women in the United States are affected by infertility. It has been estimated that approximately 80 million people worldwide are affected by infertility (Barrett, 2006). RESOLVE: The National

Infertility Association (2015), explained infertility doesn't have a preference on race, gender, or socioeconomic status although Wu et al. (2012) argued that the cost of infertility treatments may be a burden for many of the couples limiting those who seek medical help.

The most common etiologies for female specific infertility are related to blocked fallopian tubes, endometriosis, elevated levels of follicle stimulating hormone (which represents a possible decrease in a woman's ovarian function) and polycystic ovarian syndrome (Rice et al., 2015). Female infertility however is not limited to those etiologies listed above. In less frequent cases, although still prevalent, women may experience premature ovarian failure or be diagnosed with "unexplained infertility", which represents a classification of the disease in which no cause can be identified (Rice et al., 2015). Up to 10% of infertility cases cannot be explained medically (Barrett, 2006).

Nearly half of all couples shown to have an infertility diagnosis have a partner with male factor infertility (Shakkebaek et al., 1994). Male factor infertility is said to be responsible for 20-30% of all infertility cases (Agarwal et al., 2015). Approximately 10 to 15% of these male infertility cases, can be attributed to genetic causes including chromosomal abnormalities and single-gene mutations (Pizzol et al., 2014). A large proportion of male infertility however does not have a clear diagnosis and these cases are then recorded as idiopathic or unexplained infertility (Pizzol et al., 2014).

Assisted Reproductive Technology

An RE can perform any number of ART. ART comprises all procedures and/or treatments that include the in vitro handling of both sperm and human oocytes, or

embryos with the intent of establishing a pregnancy (Zegers-Hochschild et al., 2009).

Such procedures can include IVF, gamete intrafallopian transfer, zygote intrafallopian

transfer, gamete and embryo crypopreservation, gestational surrogacy, etc (Victorian

Assisted Reproductive Treatment Authority, 2015). According to data from the National

Survey of Family Growth, the percentage of women aged 15–44 who had ever used

infertility services increased from 9% in 1982 to 12% in 2006–2010 (U.S. Department of

Health and Human Services, 2005). According to Chandra et al., (2014) approximately

290,000 U.S. women between the ages of 22-44 underwent the IVF procedure between

2006 and 2010. However, the success of IVF cycles remains low (Shen et al., 2015;

Wang et al., 2009; Vahratian, 2008) and the options for women who undergo several IVF

cycles without success remain unsatisfactory (Dieterle et al., 2006; Fogarty & Smith,

2016; Shen et al., 2015). For the purposes of this study, I focused on women seeking the

aid of reproductive technologies by way of IVF.

In Vitro Fertilization: How It Works

IVF is a specific type of ART. IntegraMed America, (n.d.) explained there are

four major steps in the IVF process. The first is ovulation induction. During this phase,

fertility medications are used to increase egg production within the ovaries (Shady Grove

Fertility, n.d.). In an effort to encourage the growth of multiple follicles, which can

potentially house an egg, subcutaneous injectable are used to stimulate growth with the

aim of having the number of mature eggs greater than what would be present during a

regular menstrual cycle (Genetics & IVF Institute, 2017). This step in the process takes

between 8-14 days during which time the women is be closely monitored for follicle

growth and hormone levels (Monash IVF, 2017). Once most of the follicles are deemed "mature" by the physician, a final inject is given to trigger ovulation (Genetics & IVF Institute, 2017; Shady Grove Fertility, n.d.).

Step two of the IVF process involves the collection of the egg(s) (also referred to as the egg retrieval process). During this phase, with ultrasound guidance, a thin needle is passed through the vaginal wall into the multiple follicles of each ovary (Monash IVF, 2017). The doctor withdraws the fluid contents of each follicle and an embryologist examines the fluid to identify any mature oocyte (eggs) are present (Genetics & IVF Institute, 2017). The oocytes are then immediately isolated from the surrounding follicular fluid, placed into a culture dish, and moved to the incubator (IntegraMed America, n.d.).

Step three of the process encompasses the fertilization of the collected egg(s) whereby sperm and egg are joined, incubated, and closely monitored for successful embryo development (Shady Grove Fertility, n.d.). In the majority if IVF cycles 5-day-old embryo(s) are selected for transfer (Genetics & IVF Institute, 2017). The final stage of the IVF process is the embryo transfer, whereby a catheter containing the embryo (or some cases multiple embryos) is inserted through the cervix (IntegraMed America, n.d.). The physician then carefully places the embryo(s) along the uterine wall where implantation has the greatest opportunity (Shady Grove Fertility, n.d.).

Succeeding the transfer, a woman may be required to continue progesterone therapy to help prepare the uterine lining for implantation (Shady Grove Fertility, n.d.). Approximately two weeks following embryo transfer a blood test to measure human

chorionic gonadotropin (hCG), the pregnancy hormone, is collected (Monash IVF, 2017). It is at this stage that a women is notified if her IVF cycle resulted in a pregnancy. If a pregnancy is detected, the hCG levels will continue to be monitored for several days to ensure the pregnancy is progressing as it should before a woman will *advance* to the care of an Obstetrician (Genetics & IVF Institute, 2017)

In Vitro Fertilization Outcomes

It is commonly accepted that successful implantation requires the presence of a receptive endometrium, a functional embryo, and acceptable communication between embryonic and maternal tissue (Simón, Martín, & Pellicer, 2000). Implantation of an embryo into the uterine lining is one of the most critical steps for the success of any assisted reproductive technology (Fanchin, Righini, Olivennes, Taylor, De Ziegler, & Frydman, 1998; Roque, Lattes. Serra, Solà, Geber, Carreras, & Checa, 2013). It is during embryo transfer phase of the IVF process that the fertilized embryo (most often a blastocyst at this stage) comes in contact with, and connects to, the endometrium (Achache & Revel, 2006). In the traditional fertility cycle, the window of implantation occurs between days 19 and 21 (Díaz-Gimeno, Horcajadas, Martínez-Conejero, Esteban, Alamá, Pellicer, & Simón, 2011). Embryo implantation involves a complex sequence of events each of these signaling events offers opportunities for failure (Achache & Revel, 2006). de los Santos, Mercader, Galán, Albert, Romero, & Pellicer, (2003) concluded, implantation failure remains a major contributing factor to the cause of infertility in *healthy* women and contributes to the approximate 70% failure rate of embryo implementation following the IVF procedure . Simón, Moreno, Remohí, and Pellicer,

(1998) add, it is this inadequate uterine receptivity that is responsible for nearly two-thirds of all implementation failures.

Although numerous improvements have been made to the ovarian stimulation process, the media and environment in which the embryos are matured before transfer, and in the transfer technique itself, a significant increase in the implantation rate has yet to be seen (So et al., 2009). Implantation rates have continued to hover around 30% (Ferraretti et al., 2013; Vahratian, 2008), meaning even if a women undergoes the IVF procedure there is approximately a 70% chance that it will not be successful and repeated attempts will be necessary (Evers, 2002).

Although IVF outcomes are most often reported in generalized statistics results of studies show evidence that significant racial disparities in IVF outcomes exist (Huddleston et al., 2010; McQueen et al., 2015). Women who have a resulting live birth following the IVF procedure are disproportionately Caucasian and report both high education and income (Katz, Nachtigall, & Showstack, 2002). Not unlike race, the age of the women undergoing IVF is also a strong predictor in the success she will or will not achieve (Shapiro et al., 2016). The success of an IVF procedure decreases markedly with age (Gleicher, Kushnir, Weghofer, & Barad, 2014). Humphries et al. (2016) explained that the knowledge of these IVF outcome disparities could assist in decision making and aid treatment modifications.

Race. Various publications commented on trends that racial disparities in IVF outcomes exist (Baker et al, 2010; Fujimoto, Luke, Brown, Jain, Armstrong, Grainger, & Hornstein, 2010; Huddleston et al., 2010; McQueen et al., 2015; Seifer, Frazier, &

Grainger, 2008). An Analysis of the Society of Assisted and Reproductive Technology

(SART) 2006 dataset conducted by Purcell Schembi, Frazierm, Rall, Shen, Croughan,

Grainger, and Fujimoto (2007) found Asian ethnicity to be an independent risk factor for

poor IVF outcomes. In their study, Asian women were shown to have a decreased clinical

pregnancy rate with an odd ratio of 0.71 (95% CI = 0.64-0.80). When Asian women were

able to achieve a pregnancy following the IVF procedure, they also had a decreased live

birth rate (OR = 0.69, 95% CI = 0.61-0.77) (Purcell et al., 2007). McQueen et al. (2015)

provided evidence that the clinical pregnancy rate for Asian women was significantly

lower than in White women (31.4% vs. 36.2%; P=.04). Humphries et al. (2016) agreed

that Asian women have both lower clinical pregnancy rates and live birth rates after IVF

when compared with White women.

The 2006 Society of Assisted and Reproductive Technology (SART) dataset was

again analyzed, this time comparing IVF outcomes between Black and White women.

The data again showed disparities among the racial groups presenting the relative risk of

not achieving a live birth to be 1.21 for Black women compared to that of White women

(Seifer et al., 2008). Outcomes in the study conducted by McQueen et al. (2015) showed

a significant reduction in pregnancy rate for Black women when compared to White

women after controlling for various confounders (24.4% vs. 36.2%, P-.001).

Reasons for theses racial disparities remain unknown. However, it has been

hypothesized to be related to access to care (Feinberg, Larsen, Catherino, Zhang, &

Armstrong, 2006). A study conducted by Feinberg et al. (2006) attempted to remove the

socioeconomic barriers by reviewing the minority utilization of ART procedures in the

military health care system and to investigate if disparities were still present. The authors hypothesized those in the military (and their families) would have equal access to the infertility care regardless of race. Therefore, in this setting, the socioeconomic status confounders would be removed and any present racial disparity in outcomes could be investigated objectively. The conclusions of the study was when the access to care improved, more African American women sought assistance and even with the same access to care, African American women experienced higher rates of spontaneous abortions when compared with Caucasian women (25% vs 15.9%, RR 1.57, 95% CI = 1.05- 2.36) (Feinberg et al., 2006).

Sharara and McClamrock (2000) argued, fully understanding racial disparities present in IVF outcomes is critical in giving care. They explained that knowledge of these disparities would allow for, and encourage, alterations in clinical care and/or the IVF protocols. With future studies continuing to outline the racial disparities present in IVF success, this customized therapy may improve the reproductive outcomes specific to individual populations (Sharara & McClamrock 2000).

Age. Like race, there is disproportionate success following IVF procedures when age is applied as a variable. Despite reduced odds of success Gleicher et al. (2014) report an increase in the volume of "older" patients seeking IVF. A meta-analysis conducted in 2010 identified the most important predictor in IVF success as age (Razi, Razi, Sabeti, Ghasemi-Esnaukabad, & Pourmasumi, 2014; van Loendersloot, van Wely, Limpens, Bossuyt, Repping, & van der Veen, 2010). Kedem, Haas, Geva, Yerushalmi, Gilboa, Kanety, Hanochi, Maman, and Hourvitz, (2013) echoed this sentiment and reported most

influential confounding factor on IVF success is the age of the women. Female age has

not only been shown to be an important predictor in overall IVF success, female age is a

good predictor of poor performance at every stage of treatment (Bhattacharya,

Maheshwari, & Mollison, 2013).

Data provided by Klonoff-Cohen and Natarajan (2004) found maternal age to

have an inverse relationship with the reproductive outcomes of the IVF procedure. The

authors found a 16% increase odds (95% CI = 1.05-1.28, p =.003) of not achieving a

pregnancy for each additional year of maternal age. If the IVF was *successful* and a

pregnancy results, a 19% increased odds (OR= 1.19, 95% CI = 1.06-1.34, P= .003) was

detected of not having a live birth with each additional year of maternal age (Klonoff-

Cohen & Natarajan, 2004). Further studies conducted by Shapiro et al. (2016) provided

statistics that showed a decline in implantation rates during fresh embryo transfers from

39.9% in women younger than 35 to 2.3% in women over 44 years of age with relative

risk of 0.99. Data collected from this retrospective cohort study provided additional

information that could be used in the development of treatment plans for women of

various age groups seeking reproductive assistance by way of IVF.

Covariates. As the numbers of IVF cycles per patient increases, the outcome is

said to increase (Croucher, Lass, Margara, & Winston, 1998; Myers, 2015). A review by

Myers (2015) found that that the average success (defined by live birth) of a first time

IVF cycle is 29.5 % (95% CI = 29.3%-29.7%). The reported success of the fourth cycle

was an estimated 46.1% (95% CI = 45.8% - 46.3%). This data supported theories that as

the number of attempts to achieve pregnancy though means of IVF increase, so will the success rates.

Croucher, Lass, Margara, & Winston, (1998) found women whom had achieved a pregnancy in a prior IVF cycle are reported to have a better prognosis during subsequent attempts to have additional children. Of the women who achieved a clinical pregnancy during their first IVF cycle, the reported percentage of clinical pregnancy's in a second IVF cycle were approximately 33%. Additionally, the authors found cumulative pregnancy rates continued into the six cycle with nearly a 72% chance of success (Croucher, Lass, Margara, & Winston, 1998).

Acupuncture

Chinese medicine often defines health as dependent on the freedom and ease of the flow of both Qi (pronounced chee) and blood throughout the body (NorthStar Natural Medicine, 2010). Chinese medical theory also explains disharmonies result from an imbalance of opposing forces referred to as yin and yang (Middleton, n.d.). Middleton (n.d.) added, it is this imbalance that impedes the bodies' flow of qi that should run fluidly along the meridian pathways. The Kootenay Columbia College of Integrative Health Sciences (n.d.) related meridians to rivers and explains the meridian system is something like an energetic distribution network. It is within these meridians that qi flows. Acupoints are specific locations along the meridian path that have been identified as access points to the flow of Qi in the body (Kootenay Columbia College of Integrative Health Sciences, n.d.). Open meridians are said to be essential for optimal health (California State Oriental Medical Association, n.d.).

The aim of acupuncture is to correct any imbalance or disharmonies in both the mind and body by promoting the free flow of both these elements (blood and Qi) (Kootenay Columbia College of Integrative Health Sciences, n.d.; NorthStar Natural Medicine, 2010). Acupuncture allows the flow of Qi to area where Qi is limited and away from areas where it is in excess (California State Oriental Medical Association, n.d.). To improve the flow of Qi, needles that are approximately the diameter of a human hair are placed into and manipulated within the energy meridians found on the body (NorthStar Natural Medicine, 2010). It is believed that acupuncture works because manipulation of needles within these energy meridians removes any blockage that is preventing the optimal flow of blood and Qi (Middleton, n.d.; NorthStar Natural Medicine, 2010). With appropriate quantity and quality of treatment, the flow if Qi and energy factors such as yin and yang are brought back into balance and can restore health (NorthStar Natural Medicine, 2010). Acupuncture is argued to activate the body's own healing powers by increasing blood flow which encourages the delivery of oxygen, nutrients, analgesics, hormones, pain relieving substances, and anti-inflamomatories (Middleton, n.d.).

Acupuncture to Treat Infertility

Various treatments and preventative measures are in practice to preserve fertility and to treat those diagnosed with infertility. Acupuncture has current, intent to treat, applications for fertility issues (Anderson, Haimovici, Ginsburg, Schust, & Wayne, 2007; Dieterle et al., 2009; Qu et al., 2014). Acupuncture treatments have been used to manage infertility symptoms such as ovulatory disorders, male infertility, stress, and anxiety with studies showing various health benefits of its use (Jo, Lee, & Lee, 2015; Johansson et al.,

2013; Dieterle et al., 2009; & Qu et al., 2014). Scientist have documented increased endometrium receptivity following acupuncture (Chien, Au, Chen, Xiao, & Tzeng, 2002). Additionally, acupuncture has revealed its ability to improve menstrual frequency in women with ovulatory disorders such as polycystic ovary syndrome, a documented cause of infertility (Johansson et al, 2013). In men, acupuncture has been shown to increase testicular blood flow (Cakmak, Akpinar, Ekinci, & Bekiroglu, 2008) and recorded as having a significant effect on the total number of motile sperm (Dieterle et al., 2009). In both genders, acupuncture has been shown to reduce stress and anxiety (Qu et al., 2014) all of which have been hypothesized as an influencing factor on one's fertility (Johansson et al., 2013; Barr, Smith, & de Lacey, 2016; Buck Louis et al., 2011).

Acupuncture through the IVF cycle. Middleton (n.d.) explained any benefit of acupuncture treatment is cumulative and therefore treatment of acute conditions can take between four and eight treatments while chronic conditions can take longer to respond. With this understanding, Middleton (n.d) added it is her preference to have IVF patients start acupuncture treatments two to three months prior to the IVF procedure in an effort to resolve any underlying condition. During these sessions an acupuncturist can focus on underlying known and suspected conditions, as well as, any symptom the woman is experiencing.

Studies suggest various mechanisms that attempt to explain how acupuncture applied along with the IVF protocol can increase pregnancy (Anderson, Haimovici, Ginsburg, Schust, & Wayne, 2007). One such mechanism encompasses the stimulation of β endorphin levels. It is well accepted that β endorphin levels influence the secretion of

hormones that aid in the regulation of a woman's menstrual cycle and ovulation (Chuong, Smith, & Tsong, 1989; Stener-Victorin et al., 1996). Acupuncture protocols are in place to help correct any β endorphin imbalance (Anderson, Haimovici, Ginsburg, Schust, & Wayne, 2007; Chang, Chung, & Rosenwaks, 2002; Paulus et al., 2002).

The IVF procedure has been described as "grueling" for the patient as it involves numerous injections and the side effects associated with both the drug and the injection itself, the hectic hormone level monitoring and follicular growth monitoring that require clinic visits, as well as the financial pressure tied to each IVF cycle (Rosenthal & Anderson, 2007; Wu et al., 2012). Each of these factors can influence emotional stress levels which has been shown to inversely influence fertility (Barr et al., 2016; Buck Louis et al., 2011; Johansson et al., 2013; Ng, So, Gao, Wong, & Ho, 2008). With the addition of other acupoints, an acupuncturist can assist a women in reducing her anxiety thereby, increase the odds of pregnancy (Isoyama, Cordts, De Souza, De Almeida, Matsumura, & Barbosa 2012; Huang & Chen, 2008; Rosenthal & Anderson, 2007; Qu et al., 2014). The goal of any IVF procedure is a live birth. Studying adjunct therapies that increase the likelihood of success following IVF may in time, influence the standard protocols.

Acupuncture pre- and post-embryo transfer only. The implantation of the embryo(s) during the embryo transfer is said to be the greatest limiting factor on the success of an IVF cycle (Steer, Lin Tan, Dillon, Mason, & Campbell, 1995). Poor uterine perfusion has been shown to hinder the implantation of embryo(s) and contributes to causes of infertility (Goswamy, Williams, & Steptoe, 1988). Acupuncture protocols developed around pre- and post-embryo transfers have a strong focus on increasing blood

supply and uterine receptivity (Chang et al., 2002; Domar, Meshay, Kelliher, Alper, & Powers, 2009; Westergaard et al., 2006). Acupuncturist focus on underling factors that may contribute to infertility such as endometrial receptivity by way of increasing uterine blood flow, reduction in spasms, regulation of the menstrual cycle with changes in hormones, inner optimism, sense of relaxation, and stress reduction (Chang et al., 2002; di Villahermosa et al., 2013; Domar, Meshay, Kelliher, Alper, & Powers, 2009; Stener-Victorin et al., 2006). A healthy blood supply is an essential requirement for *normal* implantation (Jinno, Ozaki, Iwashita, Nakamura, Kudo, & Hirano, 2001; Ng, So, Gao, Wong, & Ho, 2008). Blood flow impedance within the uterine arteries has been used to measure endometrial receptivity (Stener-Victorin et al., 1996). It is understood within the infertility community that one element of a successful IVF cycle is optimal endometrial receptivity at the time of embryo transfer (Dieterle et al., 2006; Jinno et al., 2001). Scientist have documented increased endometrium receptivity following acupuncture (Chien, Au, Chen, Xiao, & Tzeng, 2002). Acupuncture treatments performed at times adjacent to the embryo transfer focus on just that.

Other researchers argued that another factor that may influence the success of IVF is the frequency of uterine contractions (Fanchin, et al., 1998). Ayoubi, Epiney, Brioschi, Fanchin, Chardonnens, and de Zigler (2003) explained that the post ovulation uterine environment is different between the uterine environment of women whom completed an IVF cycles and natural menstrual cycles. The authors stated when compared to natural menstrual cycles, the relaxed state of the uterus occurred 2 days later for those women whom were completing an IVF cycle. Fanchin et al., (1998) believed uterine contractions

negatively influences implantation of embryos during the IVF process by potentially expelling the embryo out of the uterine cavity. Therefore, suggesting that methods to reduce the frequency of uterine contractions during this time period of the IVF cycle would increase pregnancy rates following the IVF procedure. Again, acupuncturist protocols are in place to aid in relaxation of uterine walls and to reduce the frequency of contractions (Paulus et al., 2002). Performing acupuncture pre- and post-embryo transfer only may be enough to both correct any imbalance in blood flow and to reduce uterine contractions thereby increasing the odds of pregnancy following IVF.

As described above, literature is present that supports the addition of adjunct acupuncture therapy to the IVF procedure. The believed mechanisms by which the adjunct acupuncture therapy improves IVF outcomes vary. In the retrospective cohort study I aimed to determine if one form of adjunct acupuncture treatment results in a higher likelihood of success following the IVF procedure.

Current Literature Weakness

Various studies considered how acupuncture can be applied to the IVF procedure. However, many were designed in such a way that it is difficult to take the data and make it generalizable (Hullender Rubin et al., 2013). Although various meta-analysis attempted to control for these variations in various studies, weaknesses still excited (Manheimer et al., 2008; Shen et al., 2015).

One major limitation identified in the attempts to generalize numerous acupuncture protocol conclusions was the lack of a standard acupuncture protocol being performed between the studies (Zheng et al., 2014; Meldrum et al., 2013). Researchers

have had a difficult time making generalizable conclusions from current research because existing studies focused on acupuncture treatments, have variations in reported acupoints, as well as, variations in the duration of each session, timeline for overall treatment, (He, Tong, Zhao, Zhang, Ben, Qin, Huang, & Rong, 2013). Other studies, as identified in a meta-analysis conducted by Manheimer et al. (2008) lacked the appropriate number of participants. Meldrum et al., (2013) reasoned that more studies are warranted that target enrollment based on sample size calculations with a 10-20% increase in current delivery rates. A lack of consideration of confounding factors was identified in another retrospective chart review (Hullender Rubin et al., 2013). So et al. (2009) argued additional weakness in much of acupuncture research is the difficulty in achieving participant blinding. Others agreed, a fundamental design flaw is present in placebo controlled acupuncture studies because even the "controls" are likely to have physiological effects (Hullender Rubin et al., 2015).

Current literature regarding acupuncture as adjunct therapy to IVF has many weakness. Additional research is needed to control for the type of acupuncture that is applied, the timing of treatments, as well as, take into consideration confounding variables. Considerations need to be in place to limit the possibility of the placebo effect influencing the data and thereby influencing the conclusions that are drawn. By accounting for these variations, new study results may become more generalizable to the infertile community.

Summary and Conclusion

Despite advancements in infertility treatment, the success of the IVF procedures alone continues to be unsuccessful (So et al., 2009). Even when successful, success following an IVF cycle is disproportionately found in Caucasian women (Baker et al, 2010; Katz, Nachtigall, & Showstack, 2002; McQueen et al., 2015). Even still, the odds of success are greatest among younger women (Gleicher et al. 2014; Razi, Razi, Sabeti, Ghasemi-Esnaukabad, & Pourmasumi, 2014; Shapiro et al. 2016).

Many couples having difficulty conceiving have turned to ART techniques such as IVF for assistance in achieving a pregnancy (U.S. Department of Health and Human Services, 2005). With nearly 290,000 U.S. women undergoing the IVF procedure (Chandra et al., 2014), it is unfortunate that the success rates remain low (Shen et al., 2015; Wang et al., 2009; Vahratian, 2008). Acupuncture has been used for thousands of years (Zheng et al., 2012). Its uses have included the management of and treatment of subfertility (Ng, So, Gao, Wong, & Ho, 2008). In an effort to increase their odds of success, couples have sought out complementary and alternative medical treatments such as acupuncture to increase the success rate of IVF (Zheng et al., 2012).

Grounded on the presented articles in Chapter 2, it is apparent that more studies are necessary before conclusions as to the optimal adjunct acupuncture treatment is identified. Acknowledging that disparities in IVF success are present, and identifying if any adjunct therapy can close these gaps may allow for those whom have disproportionally been unsuccessful to find a better, more personalized, treatment plan, with better odds of a resulted pregnancy.

In Chapter 3, I explained the research design as well as, the rational for its use. I provided more details about the study and deliver descriptions of the independent and dependent variables. Additionally, I elaborated on the source of the data and explained the techniques used for data analysis.

Chapter 3: Research Method

Introduction

The primary purpose of this retrospective cohort review was to compare the effectiveness of two adjunct acupuncture exposures on IVF outcomes. More specifically, in this research study I examined the pregnancy outcomes following IVF when a woman receives one of two types of adjunct acupuncture treatment. The referent group or the nonexposed group—the group following standard protocol adopted in the discipline— were women whom had received IVF with a series of acupuncture treatments, more than five acupuncture treatments up to and including embryo transfer during a single cycle. The exposed group included women who received acupuncture treatments pre- and post-embryo transfer only—an adjusted protocol aimed to treat the uterine environment specifically—for a total of two treatments within a cycle.

In this chapter, I discuss the research design and the rationale for using such a design. I define the population to be studied and the procedures used to select the number of patient charts to be reviewed. I discuss the source of the data used and the collection process. I discuss the variables collected along with the analysis plan. I also discuss ethical considerations and threats to validity given the study design. The last part of his chapter summarizes this chapter and introduces the next.

Research Design and Rationale

For this retrospective cohort review, I collected and analyzed secondary data. Because pregnancy is defined as the dependent variable and the population is that of women struggling to conceive, it would not be ethical to interfere with the course of

treatment prescribed by the treating physician. Similarly, as stress has been identified as a contributing factor to reduction in pregnancy rates (So et al., 2009; Barr et al., 2016), it is not appropriate to introduce any additional stressors to women and couples undergoing the IVF procedure by way of additional variable collection or randomization which may be present in a prospective trial.

The independent variable for the primary research question was the type of adjunct acupuncture exposure received, being in the exposed or nonexposed group defined earlier. The referent or the nonexposed group was defined as five or more acupuncture treatments up to and including embryo transfer during a single IVF cycle. The exposed group was defined as having received a single acupuncture treatment prior to embryo transfer and an acupuncture treatment following embryo transfer (one pre- and one post-embryo transfer). Pregnancy outcomes (yes/no), as reported by the patient no later than 9 weeks post-embryo transfer was the dependent variable. Both patients' race and age were also collected. Race was defined using guidance from the U.S. Food and Drug administration. The following racial categories were used: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, or White (U.S. Food and Drug Administration, 2016). Hispanic ethnicity was also collected if present in the medical record and was identified as the sixth racial category. Age was collected using the following categories: 25-29, 30-34, 35-39, and $\geq$40. If available, I would have recorded if a previous IVF attempt was made. This variable would have been treated as a confounding variable.

This study design was the most appropriate choice to compare the effectiveness of two adjunct acupuncture exposures on IVF outcomes because not only did the existing medical records already contain required time-specific variables but many benefits were present due to its retrospective nature. Using secondary data was not only more time efficient for me as the researcher, but more cost conscious as well (Creswell, 2014). The dependent variable for the research was that of patient reported pregnancy outcome. Under a prospective study design, a researcher would need to follow/observe each participant for a minimum of 14 weeks to collect the type of adjunct acupuncture exposure received but also the outcome of the treatment 9 weeks post-embryo transfer. Existing datasets also offer enough medical records for review so that appropriate sample size can be obtained (Creswell, 2014). Furthermore, a logistic regression was completed to explain the relationship the independent variables have on the pregnancy rates.

Table 2

Table Summary of Nonexposed and Exposed Groups

Exposure level	Referent group	Number of adjunct acupuncture treatments per embryo transfer	Timing of adjunct acupuncture treatments
Non-exposed	Yes	≥ 5	During a cycle up to and including embryo transfer
Exposed	Non-referent group	$= 2$	Pre- and post-embryo transfer (within 72 hours of transfer)

Methodology

Eastern and Western medicine have historically been at odds with one another (Ventola, 2010). Specifically, there has been some distrust in the reported outcomes that result from Eastern medicine by the Western medical community (Frass et al., 2012; Ventola, 2010). It was hypothesized that as a result of this friction between the two approaches, adjunct acupuncture is unlikely to be captured in the clinically-based medical records of the IVF clinic. Given the study questions, it was most feasible to obtain all the required variable data from the patient charts found at the acupuncture clinic.

Population

Data was collected from existing medical records found in acupuncture clinics. The patient charts/medical records of women having received adjunct acupuncture therapy while seeking pregnancy via the IVF procedure were eligible for inclusion in this study. Each of the selected records must have had all the variables present and collected within the specified time frame.

Sampling and Sampling Procedures

The records selected for review included a minimum of four variables. The women's age during the IVF cycle (in which acupuncture exposure was completed) must have been present the patient chart. The racial identification of each patient must also have been captured in each medical chart. The type of acupuncture exposure received, that is, the number and timing of each acupuncture exposure as it related to the embryo transfer must have been documented. Finally, the outcome of the IVF cycle must also

have been recorded, that is, whether by 9 weeks post-embryo transfer the patient reported the outcome of the IVF procedure.

Advancement in the IVF procedure occur as improvements in the procedure itself as well as an increase in the knowledge within the field (Wade, MacLachlan, & Kovacs, 2015). In an attempt to control for the possibility of an increase in IVF success independent of any adjunct therapy, only medical records of patients who have received adjunct acupuncture exposure and undergone the IVF procedure within the last 5 years of the Institutional Review Board (IRB) approval date were studied. I reviewed patient charts from the most recently completed IVF cycle (embryo transfer plus 9 weeks for results) through older records until enough medical records had been reviewed to meet the calculated sample size. For the record to have been eligible for review, the IVF cycle must have occurred within the 5-year window.

Using G*Power as a tool to assist with sample size calculations, the appropriate sample size of 420 patient charts was calculated. Therefore, approximately 210 medical records were needed to be reviewed from each the nonexposed and exposed group. This number was derived by imputing an alpha level of 0.05, power at 80%, and an odds ratio of 1.885. The odds ratio used in this calculation was an average of two similar articles published in 2012 and 2016 (Hullender Rubin et al., 2012; Hullender Rubin et al., 2015).

Permission for Data Collection

For the research I first had to identify which acupuncture clinics had the required data and were willing to share the client records. Via cold calls, I requested to talk to staff of the acupuncture clinics to confirm which types of acupuncture were performed as a

standard clinical practice and what variables were collected in medical records. Of those

clinics that qualified, a further discussion of the doctoral research project ensued. If the

clinic appeared interested in participating, I explained the requirement of an IRB

permission to move forward and explained the volume of charts necessary to review. I

had prepared a plan that if single clinic did not have all the proposed 420 medical charts,

I would continue to search for other willing clinics to collect remaining records. I had

decided if after 10 clinics had been contacted that had either not met the requirements or

had not shown an interested in participating, I would request publication of an

advertisement to the acupuncture community via a journal. This advertisement would

have introduced the study and requested willing clinics to participate.

Following an e-mail introduction of both myself and the anticipated study design,

an acupuncturist had expressed interest in collaborating. The acupuncturist explained he

was the founder of a collection of acupuncture clinics. The acupuncturist further

explained that the required 420 medical charts would not likely be found in a single

location. The founder of the acupuncture clinics instead offered access to the records of

multiple clinics. Each of these clinics were under the same business name as well as

under his leadership. Following the selection of participating sites, I confirmed Walden

University would be the IRB of record and an application was submitted to Walden IRB

for permission to collect data from the various participating acupuncture clinics.

Prior to collecting any data, I obtained an IRB approval from Walden University.

Due to the retrospective nature of the study, I requested a waiver of consent allowing for

review of existing data (collected for purposes other than research), without the added

requirement of participants' written consent. The founder of the participating acupuncture clinics in which the data was extracted provided a data use agreement to the IRB of record. I also signed a business use agreement between the clinic and myself providing permission to review existing medical records/patient charts from the selected acupuncture clinics. Upon receipt of the IRB approval letter, signed data use agreement, and signed business agreement, data collection began.

Data Analysis Plan

I collected retrospective data from approved acupuncture clinics. The association between the type of adjunct acupuncture exposure received (the independent variable) and pregnancy (the outcome) was determined via binary logistic regression using SPSS software. This section restates the research questions, describes the statistical procedures, offers the rationale for the sample size, and provides a brief description of the validity of the research design.

Research Questions and Hypotheses

RQ1: Is receiving acupuncture pre- and post-embryo transfer associated with pregnancy?

$H_0 1$: Receiving acupuncture pre- and post-embryo transfer is not associated with pregnancy.

$H_a 1$: Receiving acupuncture pre- and post-embryo transfer is associated with pregnancy.

RQ2: Is receiving acupuncture pre- and post-embryo transfer associated with pregnancy when controlling for age of women?

$H_0 2$: Receiving acupuncture, pre- and post-embryo transfer is not associated

with pregnancy when controlling for age of women.

$H_a 2$: Receiving acupuncture pre- and post-embryo transfer, is associated with

pregnancy when controlling for age of women.

RQ3: Is receiving acupuncture, pre- and post-embryo transfer associated with

pregnancy when controlling for race of women?

$H_0 3$: Receiving acupuncture, pre- and post-embryo transfer is not associated

with pregnancy when controlling for race of women.

$H_a 3$: Receiving acupuncture pre- and post-embryo transfer is associated with

pregnancy when controlling for race of women

Analysis Plan

The effectiveness of two adjunct acupuncture exposure types were analyzed using

binary logistic regression method. As listed above, the independent variables was

recorded categorically. Similarly, the dependent variable (pregnancy outcome) was

recorded categorically. The outcome was recorded as either yes or no. SPSS aided me in

performing the logistic regression. As very few variables were collected for analysis,

patient records that had missing variables were excluded from analysis. Therefore, no

additional statistical manipulation of the data was necessary to account for missing

variables. Patients that had records of multiple IVF attempts were not excluded and each

IVF attempt was included in analysis so long as it met the inclusion criteria and occurred

within the 5 year data collection period.

Statistical test. Because the independent variables were categorical and the dependent variable was a binary event (yes/no), logistic regression was an appropriate method for analysis (Stoltzfus, 2011). If there were a positive association among independent and dependent variables, this method would have allowed readers to conclude that pregnancy outcomes could be predicted given the type of adjunct acupuncture received. Similarly, this method had the potential to reveal any contribution of an independent variable after adjusting for the others (Stolzfus, 2011). The odds ratio was used to calculate the effect size in an attempt to determine the effectiveness (if any) that was present as a result of adjunct acupuncture exposure on IVF outcomes. Power was calculated at 80% and data was considered statistically significant if $p<0.05$. Modelling using multiple logistic regression to include all variables and to predict the most parsimonious model was conducted.

Software. Analysis of data was completed via SPSS software.

Threats to Validity

Not unlike other study designs, the retrospective cohort reviews have data limitations and assumptions must be made when analyzing collected data. External, internal, and construct validity must be considered prior to analysis and interpretation of data. Each of these concerns is discussed below

External Validity

External validity refers to how generalizable the conclusions may be (Trochim, n.d.). In general, there are three threats to external validity based on the study population (Trochim, n.d.). The results of the completed study could show significance as a result of

the sample of medical charts selected for review, the dates in which data was recorded, and/or due to the clinic setting the acupuncture or IVF procedure was performed.

Tabachnick and Fidell (2007) remind researchers that too many variables may lead to outcome(s) that are mathematically unstable and may result in decreased generalizability. The completed research contains only four required variables (age, race, acupuncture type and outcome). A fifth variable was collected when available and treated as confounding (previous IVF attempts were - collected as yes/no). Just as it was mentioned above, the IVF procedure itself has improved over the years and pregnancy rates following the procedure have increased (Wade et al., 2015).

In an effort to account for these threats to external validity, I selected medical records for review from a single acupuncture group (limiting acupuncturist treatment delivery variances). Additionally, charts were pulled for review by way of pulling the most recent record to the oldest (until the number of charts required were met). It is also important to recognize that the exact percentage of success calculated for this research dissertation is like to become outdated as further advancements are made with the IVF procedure. However, the broader conclusions of effectiveness of adjunct acupuncture to IVF outcomes may still be used.

Internal Validity

The extent to which a researcher can trust the conclusion(s) of the relationship between the independent variables(s) and dependent variable is known as internal validity (Stangor, 2011). Internal validity is relevant in study designs that attempt to establish a causal relationship (Trochim, n.d.). Trochim (n.d.) added, for studies where the effects of

interventions are studied, internal validity should be a primary consideration of a study. Internal validity comes into play when a researcher looks to uncover why an outcome of a study may be present. That is, did the "intervention" caused the outcome or was the outcome a result of some other confounding variable?

The completed study used retrospective data. Therefore, I did not give an intervention to the study population rather, she categorized the existing records of patients into one of two groups. Those whom have received more than five acupuncture treatments during a single IVF cycle or those whom have received two adjunct acupuncture treatments (one before embryo transfer and the second after).

The history threat of internal validity suggested that some event has influenced the outcome (Stangor, 2011). Just as was described above, an improvement in the IVF procedure may result in more positive pregnancy outcomes than was historically recorded. In an effort to limit this historical threat on internal validity, only record within the past five years were eligible to be included in the dataset.

Pregnancy test are not given in the acupuncture clinic. Therefore, the outcome/dependent variable (i.e. pregnancy results), that were present in the acupuncture clinic notes were patient reported. Recall bias is always a potential concern when asking a person about past test results (Creswell, 2014; Frankfort-Nachmias, & Nachmias, 2008). However, the acupuncturist's follow-up to the individual occurred during the time in which a woman, if successful, would still be pregnant. Therefore, the women would not need to *recall* the results of her test rather, she at the time, was reporting on her current pregnancy status.

Ethical Procedure

For this project, pregnancy was defined as the dependent variable and the population was that of women struggling to conceive. Therefore, it would have not be ethical to interfere with the course of treatment prescribed by the treating physician. There was no attempts to contact women who had sought any ART procedure. Similarly, as stress has been identified as a contributing factor to reduction in pregnancy rates (So et al.; Barr et al., 2016) it again, would not have been appropriate to introduce any additional stressors to women and/or couples undergoing the IVF procedure by way of requesting the collection of additional variable(s) via a randomization process which may be present in a prospective trial.

According to the Protection of Human Subjects 45 CFR part 46 (2009a), a human subject is defined as a living individual about whom a researcher obtains either data through interaction with an individual or gathers identifiable private information about an individual. The retrospective cohort review required me to review the medical records of acupuncture clinic patients. Consequently, I had access to protected health information. Prior to reviewing any patient data, I required Walden University's IRB approval. I was granted permission from Walden's IRB to review patient charts without obtaining written consent from each patient. The study was eligible for a waiver of participant consent because the four criterions necessary for such an exemption were met. The research involves not more than manual risk; the waiver did not adversely affect the rights and welfare of the subject, the research could not practicably be carried out without the waiver, and if applicable the patients will be made aware of any pertinent information

uncovered during the study (Protection of Human Subjects, 2009b). In addition to the IRB approval, I also requested letter of support from the acupuncture clinic prior to reviewing any data.

Each of the patient charts reviewed was given a subject ID. This was done in an attempt to not record the same record twice. The electronic file linking the subject ID to the medical record was kept in a password protected document on a password protected computer. The data that was analyzed was stored in a non-identifiable manner. That is, only subject ID were present (none of the 18 HIPAA identifiers were in this file). When not in use, the computer holding the research files was behind a locked door.

Upon completion of the data analysis and approval of the final oral defense the document that links the subject ID to the medical record was destroyed. As no patient identifiers were present in the dataset, the dataset can be kept indefinitely. This record were shared with the acupuncture clinic in which it was collected. The unidentified dataset up to this point has not been reviewed by Walden faculty but may be reviewed by facility of Walden University and my dissertation committee and URR reviewer upon request.

Summary

Throughout this chapter an explanation of the research design and methodology was present. Rational for why the design was selected and how it related to the study questions was also discussed. Both the dependent and independent variables were reviewed and the necessary permissions to collect the selected data points were discussed. A description of where the retrospective data was collected from was provided

and justification for the statistical test along with recognition of the threats to validity and reliability for this study were reviewed. The forthcoming chapter will discuss the analysis of the data and results of the study.

Chapter 4: Results

Introduction

The purpose of this study was to compare the effectiveness of two types of adjunct acupuncture exposures on IVF outcomes by applying the concept of the epidemiology triad and analyzing data using binary logistic regression. The remainder of this chapter provides details of data collection, a description of the demographic makeup of the study sample, and a concise analysis according to each of the research questions. The conclusion of the chapter includes a brief summary of the results.

Data Collection

Data collection occurred at five participating acupuncture clinics. All required variables had been previously collected as part of usual care at each of the five participating sites. No patients were contacted for this study and only data that been previously recorded was shared with me. The five participating sites all fell under the same corporate name and allowed me to gather data that spanned the Philadelphia region. Walden University's IRB reviewed and found the study to be acceptable as a collection of a limited data set (IRB approval number 12-21-18-0135330).

An optional data collection tool was provided to each of the participating clinics (see Appendix A). This optional tool outlined the required variables that were necessary for inclusion in the analysis. Each clinic extrapolated data from existing medical charts and opted to enter data into their own Excel worksheet rather than use the optional tool. Each site then provided their Excel documents back to the founder of the participating clinics, and they were then consolidated into a single working data collection sheet. After

consolidation, this document was returned to the me for review. A total of 4,350 IVF

procedures with adjunct acupuncture records were collected and provided to me. Of those

records only 444 records met the inclusion criteria (all variables were available). These

444 records were scrubbed of any protected health information, coded, and then analyzed

using SPSS software.

Sample Demographics

Eligible records for analysis were those of women having completed an IVF cycle

with adjunct acupuncture treatment either pre- and post-embryo transfer only, defined as

the exposed group, or five or more times up to and including embryo transfer, defined as

the nonexposed group. In order for a case to be collected, all required variables must have

been available. A medical record without all required variables was excluded from

review. A total of 444 IVF cases met the inclusion criteria and were subsequently entered

into SPSS software and later analyzed.

The majority of all cases were identified as Caucasian ($n = 382$ at 86% of total

sample). The second most common group to be reported were Asian women ($n = 13$,

7%), followed by Black, Hispanic, then American Indian or Alaska Native women ($n =$

18, 4.1%; $n = 12$, 2.7%; $n = 1$, 0.2%, respectively).

When broken down by age, women between 35 and 39 years of age were the

largest sample recorded with 179 records representing 40.3% of the total sample. This

was followed by women 30 through 34 years of age ($n = 155$, 34.9%), women greater

than or equal to 40 years of age ($n = 92$, 20.7%), and lastly, women 25 through 29 years

of age ($n = 18$, 4.1%).

The frequencies and percentages of the demographics can be found in Table 3.

Table 3

Frequencies and Percentages of Demographic Features

Racial group	*N*	% of sample
Caucasian	382	86
Asian	13	7
Black	18	4.1
Hispanic	12	2.7
American Indian or Alaska Native	1	0.2
Age		
25-29	18	4.1
30-34	155	34.9
35-39	179	40.3
≥40	92	20.7

Note. ($n = 444$).

Pregnancy Outcomes

More than half of the total sample analyzed, 236 (53.2%) women, presented with

a positive pregnancy outcome following the IVF procedure with adjunct acupuncture.

The remaining 208 records showed the IVF procedure did not result in a pregnancy.

Further breakdown showed 119 pregnant women were in the exposed group (50.4% of

the total pregnant sample) while 117 cases of pregnancy were in the nonexposed group.

Results of pregnancy outcomes following the IVF procedures with adjunct

acupuncture are presented in Table 4 below.

Table 4

Pregnancy Outcomes by Exposure Level

	Positive	Negative	% of pregnancy	Asymptotic significance (2-sided)
Exposure				.306

| Exposed | 119 | 115 | 50.9% |
| Nonexposed | 117 | 93 | 55.7% |

Results

I used a series of regressions for the data analysis of each of the following research questions.

Research Question 1

RQ1: Is receiving acupuncture pre- and post-embryo transfer associated with pregnancy?

$H_0 1$: Receiving acupuncture, pre- and post-embryo transfer is not associated with pregnancy.

$H_a 1$: Receiving acupuncture, pre- and post-embryo transfer is associated with pregnancy.

The dependent variable data for the each of the research questions, pregnancy, was collected in a categorical manner. Pregnancy was recorded as either yes or no. The dichotomous nature of this variable met the assumptions of the logistic regression. Data showed there were no extreme values or outliers and therefore again confirmed the logistic regression assumptions were met.

I conducted a binary logistic regression analysis to investigate if acupuncture pre- and post-embryo transfer is a predictor of pregnancy when undergoing the IVF procedure. The outcome of interest was pregnancy status. The predictor variable for the primary research question was exposure of adjunct acupuncture pre- and post-embryo transfer. The Hosmer-Lemeshow goodness-of-fit was not significant ($p > .05$) indicating

the model was correctly specified. Additionally, the -2 log Likelihood = 612.697 and the

Nagelkerke R squared = .003. The predictor variable, exposure, was not significant at $p =$

0.306; therefore, I failed to reject the null hypothesis.

Table 5

Significance of Exposure on Pregnancy Outcomes

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I for EXP (B) Lower	Upper
Exposed	-.195	.191	1.049	1	.306	.823	.566	1.195
Constant	.230	.139	2.731	1	.098	1.258		

Research Question 2

RQ2: Is receiving acupuncture pre- and post-embryo transfer associated with

pregnancy when controlling for age of women?

$H_0$2: Receiving acupuncture, pre- and post-embryo transfer, is not associated

with pregnancy when controlling for age of women.

H_a2: Receiving acupuncture, pre- and post-embryo transfer, is associated with

pregnancy when controlling for age of women.

Analysis for the second research question was conducted using a binary logistic

regression to investigate if age is associated with pregnancy when receiving adjunct

acupuncture during the IVF cycle. The outcome of interest was pregnancy. The possible

predictor variable was age. Age was collected in categorical fashion with women 25-29

years old in one group, 30-34 years of age in another, 35-39 in a group, and the last group

was all women undergoing IVF with adjunct acupuncture who were 40 years of age or

older. The Hosmer-Lemeshow goodness-of-fit was not significant (p > 0.05) indicating

the model was correctly specified. Additionally, the -2 log Likelihood = 608.351 and the

Nagelkerke R squared = .016. The predictor variable in the analysis, age, was found to

contribute to the model. The unstandardized Beta weight for the constant was *B* = .898,

SE = .352, *Wald* = 6.495, *p* < .05. The unstandardized Beta weight for the predictor

variable was *B* = -.245, *SE* = .118, *Wald* = 4.299, *p* = .038. The estimated odds ratio

favored a decrease of nearly 21.7%, [*Exp (B)* = .783, 95% CI (.621, .987)] for every unit

of age increase. That is, to put it plainly, for every 5-year increase in age, the odds of

getting pregnant decrease by approximately 22%. The predictor variable in this case, age,

was significant at *p* = 0.038; therefore, the null hypothesis was rejected and the analysis

was in favor of the alternative hypothesis (see Table 6). I than ran additional tests with a

focus on exposure of each of the age groups separately. Results of the separate binary

logistic regressions for each of the age groups are found in Tables 7-10 below. Each of

these tables showed *p* values greater than *p* =.05 reporting there was no significant

relationship of any age group on pregnancy outcomes.

Table 6

Significance of Age on Pregnancy Outcomes

| | B | S.E. | Wald | Df | Sig. | Exp(B) | 95% C.I for EXP (B) | |
							Lower	Upper
Exposed	-.173	.192	.809	1	.368	.841	.578	1.226
Age	-.245	.118	4.299	1	.038	.783	.621	.987
Constant	.898	.352	6.495	1	.011	2.455		

Table 7

Significance of Exposure on the 25-29 Years of Age Group on Pregnancy Outcomes

| | B | S.E. | Wald | Df | Sig. | Exp(B) | 95% C.I for EXP (B) | |
							Lower	Upper
Exposed	-1.476	1.045	1.993	1	.158	.229	.029	1.774
Constant	.560	.627	.797	1	.372	1.750		

Table 8

Significance of Exposure on the 30-34 Years of Age Group on Pregnancy Outcomes

| | B | S.E. | Wald | Df | Sig. | Exp(B) | 95% C.I for EXP (B) | |
							Lower	Upper
Exposed	.031	.326	.009	1	.925	1.031	.545	1.952
Constant	.310	.229	1.831	1	.176	1.364		

Table 9

Significance of Exposure on the 35-39 Years of Age Group on Pregnancy Outcomes

| | B | S.E. | Wald | Df | Sig. | Exp(B) | 95% C.I for EXP (B) | |
							Lower	Upper
Exposed	-.080	.303	.069	1	.793	.923	.510	1.674
Constant	.280	.227	1.522	1	.217	1.324		

Table 10

Significance of Exposure on the ≥ 40 Years of Age Group on Pregnancy Outcomes

	B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I for EXP (B)	
							Lower	Upper
Exposed	-.568	.430	1.748	1	.186	.567	.244	1.315
Constant	-.095	.309	.095	1	.758	.909		

Research Question 3

RQ3: Is receiving acupuncture, pre- and post-embryo transfer, associated with pregnancy when controlling for race of women?

H_03: Receiving acupuncture, pre- and post-embryo transfer, is not associated with pregnancy when controlling for race of women.

H_a3: Receiving acupuncture, pre- and post-embryo transfer, is associated with pregnancy when controlling for race of women.

I conducted analysis for the third research question using a binary logistic regression to investigate if race is associated with pregnancy when receiving adjunct acupuncture during the IVF cycle. Race was collected in categorical fashion. Cases could be identified as one of the following, American Indian or Alaskan Native, Asian, Black, Native Hawaiian or Pacific Islander, White, or Hispanic. For this analysis White cases were identified as baseline because they represented the largest group. The outcome of interest was pregnancy status. The predictor variable was race. The Hosmer-Lemeshow goodness-of-fit was not significant ($p > .05$) indicating the model was correctly specified. Additionally, the *-2 log Likelihood = 610.675* and the *Nagelkerke R squared = .009*. The

predictor variable, race, was not significant at p = 0.964 and therefore, I failed to reject the null hypothesis.

Table 11

Significance of Race on Pregnancy Outcomes

| | B | S.E. | Wald | Df | Sig. | Exp(B) | 95% C.I for EXP (B) | |
							Lower	Upper
Exposed	-.195	.192	1.037	1	.309	.823	.565	1.198
Race			.593	4	.964			
Native Indian or Alaska Native	-21.214	40192.97	.000	1	1	.000	.000	
Asian	.246	.379	.420	1	.517	1.279	.608	2.690
Black	.104	.486	.046	1	.830	1.110	.428	2.877
Hispanic	.245	.595	.169	1	.681	1.277	.398	4.102
Constant	.206	.143	2.075	1	.150	1.229		

Summary

In this chapter, a discussion of the data collection procedures, sample demographics, and statistical analyses per research questions were discussed. The dependent variable for each of the three research questions was defined as pregnancy outcome and was a dichotomous variable in nature. Therefore, binary logistic regressions analyses were used. The first research question had a single dichotomous predictor (independent variable) and results of this analysis indicated there is no signification difference between pregnancy outcomes among acupuncture exposure level. That is, there was no difference between pregnancy outcomes in women that received acupuncture pre- and post-embryo transfer only and women that received acupuncture 5

or more times up to and including embryo transfer. The second research question showed that for every 5 year increase in age (as collected) the odds of getting pregnant decreased by 21.7%. However, when pregnancy outcome was examined for each exposed age group data showed no significance. Therefore, exposure when broken down by age group does not contribute to pregnancy. The third research question showed that there was no significant difference in pregnancy outcomes for any racial group when compared with White women. Chapter 5 will discuss the interpretation of these results, any limitations, how they apply to social change, and recommendations for action.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this study was to compare the effectiveness of two types of adjunct acupuncture exposure on IVF outcomes. I examined the association between pregnancy outcomes following IVF and two types of adjunct acupuncture, age, and race. The study was completed through a retrospective cohort review, was grounded in the epidemiology triad model, and analyzed using binary logistic regressions. As discussed in the previous chapter, the results of the binary logistic regression for RQ1 showed no significant difference between pregnancy outcomes in the exposed group (women having received adjunct acupuncture pre- and post-embryo transfer only) and pregnancy outcomes in the nonexposed group (women having received adjunct acupuncture five or more times up to and including embryo transfer). Analysis for RQ2 found the odds of IVF success in the exposed group were decreased by 21.7% when age increased 1 unit (each unit equaled a 5-year spread). Further breakdown showed no association between pregnancy outcomes and exposure on specific age groups. Lastly, the results of the binary logistic regression for RQ3 found no significant difference between pregnancy rates for women of varying ethnicities in the exposed group when compared with White women. The remainder of Chapter 5 provides an interpretation of these results and discusses any limitations. Additionally, the following chapter also provides suggestions how these results apply to social change and put forth recommendations for action.

Interpretation of the Findings

The epidemiologic triad served as the theoretical framework for this study. This research looked at the association of the various host and environment options with the agent being held constant (receipt of the IVF procedure) on pregnancy outcomes. Although originally implemented to study the cause of infectious diseases, the epidemiologic triad has been applied to noninfectious disease as well (Miller, 2002). This framework was selected as it supported the current published literature on the topic. In the case of this study, the study design collected variations of age, race, and also the type of adjunct acupuncture received to include one adjunct acupuncture protocol pre- and post-embryo transfer compared to adjunct acupuncture treatments of five or more times up to and including embryo transfer during a single IVF cycle. The outcome of pregnancy (yes/no) was then collected retrospectively. The outcomes following a change in host (age or race) or environment (exposure group: exposed or nonexposed) are found in the discussion below.

Research Question 1

The results of the binary logistic regression analysis for RQ1 did not identify a statistically significant difference between pregnancy rates of exposed versus nonexposed women. Pregnancy, as an outcome following IVF, was similar when comparing both the exposed and nonexposed groups (50% vs. 55%). There was no significant difference between the two types of exposure ($p = 0.306$). It is, however, noteworthy that in existing literature the success of an IVF cycle without adjunct acupuncture has been reported as approximately 30% (de los Santos et al., 2003; Ferraretti et al., 2013; Vahratian, 2008).

Each of the cited studies had various confounding factors such as the maturation or the quality of the embryo that was transferred (de los Santos et al., 2003). Fertility- related characteristics such as diagnosis and number of years with infertility related problems were also included in the long list of potential confounding factors (Vahratian, 2008). Furthermore, existing published literature also provides evidence that race and/or age can influence IVF outcomes (Humphries et al., 2016; & Revelli et al., 2016) and prompted the need for the second and third research questions.

  Although the data showed a nonsignificant difference between pregnancy outcomes in the exposed group and the nonexposed group (50% vs 55%), there is an obvious difference among those who received adjunct acupuncture (of any exposure level) compared with women who received IVF alone (no adjunct acupuncture). The data from this study thereby established that the type of adjunct acupuncture received is not important because receiving either type (exposed or nonexposed) would increase the odds of pregnancy from 30% (the reported outcome without the addition of adjunct acupuncture) to the approximate 50% odds of pregnancy found when adjunct acupuncture is included in the IVF protocol. Therefore, any acupuncture received would be better than not having acupuncture. It is worth noting however, that IVF without adjunct acupuncture was an exclusion criteria in this study and therefore comparisons of existing literature were necessary. The only data supported conclusion of this study is that there is no difference in pregnancy outcomes among the two exposure levels (as supported by the p value of .306). The data then further indicated that additional studies should be conducted.

Research Question 2

The age of each women during the embryo transfer was collected and recorded categorically for this project. Each category had a range of 5 years with the exception of the last category of greater than or equal to 40 years of age at the time of embryo transfer. The results of the binary logistic regression analysis for RQ2 showed a statistically significant difference between pregnancy rates when age was added as a covariate. Results of the analysis when age was entered as a covariate showed the estimated odds ratio favored a decrease of 21.7% for every unit of age increase (95% CI = 0.621-0.987, *p* =.038). Therefore, the odds of success decrease approximately 22% every five years as a woman gets older.

In Klonoff-Cohen and Natarajan's (2004) published study, maternal age was shown to have an inverse relationship with the reproductive outcomes of the IVF procedure. The authors found a 16% increase in odds (95% CI = 1.05-1.28, *p* =.003) of not achieving a pregnancy for each additional year of maternal age. It is important to recognize that the conclusions of this published study were for each year of increased age, while my analysis showed a 21.7% decrease in pregnancy outcomes for each category (up to 5-year spread).

When I completed additional regressions for each age category separately, no significance was noted. These regressions confirmed there is no significant differences among pregnancy outcomes when exposure level (exposed or nonexposed) and a specific age group is used as a covariate. The results of these test show *p* values less than .05 (*p* =

1.58 in the 20-24 age group, *p* = .925 in the 25-29 age group, *p* = .793 in the 35-39 age

group, and *p* = .186 in the ≥ 40 age group).

Age of the women undergoing IVF has been shown in the literature to be a strong

predictor in the success of an IVF cycle (Shapiro et al., 2016). As a woman becomes

older, her odds of success decrease (Gleicher et al., 2014). The results of this study

supported the existing literature as a whole in this regard. However, this study did not

provide statistically significant results in regard to each age category when reviewed

separately. An unfortunate limitation of this study's analysis is that age was analyzed

categorically while existing literature collected actual years of age. This makes

comparison between the groups slightly more challenging. Another limitation was the

number of cases reviewed. The sample analyzed did not have an even distribution of

cases among each age group. When further stratifying the sample for these individual age

group regressions, power was lost. Better powered conclusions could have been made if

each age group had 420 cases rather than the sum of all group totaling 420 (as was

determined in the sample size calculation). Further research studies are necessary that

would both collect the actual age during embryo transfer as well as increase the number

of cases reviewed.

Research Question 3

The results of the binary logistic regression analysis for RQ3 did not identify a

statistically significant difference between pregnancy rates when comparing different

racial groups to that of White women. The analyses showed all racial groups were just as

likely to have a pregnancy outcome as White women. That is, the data showed no one

group was any more likely to have a pregnancy outcome than another if receiving adjunct acupuncture.

Existing literature has acknowledged the presence of racial disparities in IVF outcomes alone (Baker et al, 2010; Fujimoto et al., 2010; Huddleston et al., 2010; McQueen et al., 2015; Seifer et al., 2008). McQueen et al. (2015) provided evidence that the clinical pregnancy rate for Asian women were significantly lower than in White women (31.4% vs. 36.2%; $p = .04$). A significant reduction in pregnancy rate for Black women when compared to White women after controlling for various confounders (24.4% vs. 36.2%, $p = .001$) was also reported by the same authors.

The analysis of data for RQ3 is not in agreement with the findings of the other study results discussed above. The data from this study provided evidence that when adjunct acupuncture is applied to the IVF protocol these racial disparities that are present otherwise are reduced. A serious hindrance in making a strong claim that receiving adjunct acupuncture would reduce the disparity of success among various racial groups is that the number of cases reviewed in each racial group was not evenly distributed. The sample of 444 cases analyzed in this study had only 62 non-White women. This represented 13.9% of the total sample population. Making conclusions on such a small number, although allowable, is subject to ridicule. When attempting to stratify the sample and run analysis on each racial group, power was lost. The promise seen in the results of these few cases reviewed did advocate for future research that would focus on recruitment of a larger sample of non-White women.

Limitations of the Study

All data was previously recorded in medical charts of patients receiving adjunct acupuncture in the Philadelphia area. Individuals working at each of the participating clinics extrapolated the necessary data and entered it into a site-specific Excel document. Site data was then given to the founder of the clinics and consolidated into a single document. The transfer of data from a medical record to a Excel document then again transferred to another consolidated document offers opportunity for various types of transcription errors. Given that all data was collected from a single region, an additional limitation of the study was that the conclusions may not be generalizable outside of the Philadelphia region.

Confounding factors such as the number of prior IVF attempts, the addition of other complementary and alternative medicine such as herbal supplements and use of various mediation techniques were not recorded in the medical charts and so were not available to me. Similarly, lifestyle factors such as alcohol intake, nicotine use, drug use, dietary habits, and physical activity level were not recorded in the acupuncture clinics' medical records and may possibly have affected the relationship between the variables in the study. (see Eugster & Vingerhoets, 1999; Peyromusavi, Barouni, Naderi, & Shahravan, 2016; Ventola, 2010; Zhang et al., 2014).

The completed study determined there was no difference in the odds of pregnancy when race was a factor. This data is contrary to existing published literature. A limitation of the completed study however was the small sample size of non-White women that represented only 13.9% of the total sample. There was only a single record from an

American Indian and there was no Native Hawaiian or Pacific Islander representation in the study sample. Therefore, no conclusions could be made about these racial groups and the effect if any adjunct acupuncture has on their IVF outcome.

Additionally, the study did not include a group of women who received IVF without adjunct acupuncture. Rather, it compared one type of acupuncture to another therefore, the interpretation of the data may be misleading as to the value adjunct acupuncture can bring to the IVF protocol. Some of my conclusions showed there was no difference between the exposed group and the nonexposed but when compared with existing published data the value of adjunct acupuncture can be more clearly seen.

Recommendations for Future Research

The analysis of the data has created additional questions. Recommendations for future studies are suggested as a result of the interpretation of study data. In an ideal scenario, a researcher would have limitless amount of time and could control for the improvement in the IVF procedure unaccompanied. As new or improved techniques of the IVF procedure are uncovered, they are often incorporated in the standard IVF protocol. Controlling for these advancements in the IVF procedure during a clinical trial that focuses on adjunct therapy would encourage a researcher to account for any success to be related to the adjunct acupuncture being studied. This however is not a possibility as we cannot/ should not slow down the advancement of a medical procedure for the purposes of researching another therapy.

The development and implementation of a randomized prospective clinical trial could also eliminate some of the limitations described in the section above including

transcription errors. In this proposed study, participants would be randomized into one of 3 groups, acupuncture pre- and post-embryo transfer only, 5 or more acupuncture treatments up to and including embryo transfer, or IVF alone (no adjunct acupuncture). In this design, the control group would be women not receiving acupuncture and more direct comparisons could be made between the 2 forms of adjunct acupuncture and the IVF procedure alone.

An additional recommendation includes enrolling matched cases in each group studied. That is, a women with the same number of IVF attempts, age, and race would be enrolled in each group. This would provide opportunities for researchers to see what the *same* woman's outcome would be if she were enrolled in any of the groups of the study. This proposed study would likely be the very challenging due the requirement of matched participants and therefore unlikely to be possible.

Although this study had data collected from acupuncture clinics that were a part of the same company and likely under the same standard operating procedures, a future recommendation is to run a similar study with the same acupuncturist performing treatment. This would limit any variations in technique that could influence outcome results.

A further recommendation is to run a similar study but focus recruitment on non-White women and to expand the catchment area of participants to include women of different regions. The analysis of this study suggested that adjunct acupuncture could reduce the racial disparities of IVF success. However, such claims are difficult to make without a larger sample of non-White women. Furthermore, the generalizability of the

study is difficult when the population sampled was collected from one area in Pennsylvania.

Lastly, in the best case scenario, each of the above recommendations could be applied in the same study. A prospective randomized matched case controlled trial design with the same acupuncturist to perform the adjunct therapy would be ideal. This design would require enrollment at least nationwide to be sure to represent the US population at a minimum, an acupuncturist to be able to travel to deliver adjunct acupuncture as needed, and require advancement of the IVF procedure to halt until enrollment in this trial was met. This, however, would be the most difficult study to achieve and likely impossible, but would help to answer some of the outstanding questions this study creates.

Implications for Positive Social Change

Identification of effective adjunctive therapies to increase the success of IVF could decrease the number of attempts necessary to achieve pregnancy and thereby increase the number of women who would find success in the IVF procedure. Implantation rates have continued to hover around 30% (Ferraretti et al., 2013; Vahratian, 2008), meaning even if a women undergoes the IVF procedure there is approximately a 70% chance that it will not be successful and repeated attempts will be necessary (Evers, 2002). Disproportionate success among different age and/or race groups have been reported for women whom have undergone the IVF procedure (Baker et al, 2010; Fujimoto et al., 2010; Gleicher et al. 2014; Huddleston et al., 2010; McQueen et al., 2015; Razi, Razi, Sabeti, Ghasemi-Esnaukabad, & Pourmasumi, 2014; Seifer, et al.,

2008; van Loendersloot, van Wely, Limpens, Bossuyt, Repping, & van der Veen, 2010).

The primary purpose of this retrospective cohort review was to compare the effectiveness

of two adjunct acupuncture exposures on IVF outcomes. Secondary objectives were to

examine the success of IVF with adjunct acupuncture when accounting for age or race.

Analysis of the data collected for this study showed there is no significant

difference between pregnancy outcomes in the exposed and nonexposed groups. That is,

the type of exposure does not contribute to pregnancy. This is however, a reported

reduction in odds of pregnancy when age is increased. This supported existing

publications that stated as one ages, pregnancy outcomes are reduced. Conversely,

additional analysis that examined IVF outcomes with exposure level in each age group

resulted in a non-significant value further supporting that the type of exposure does not

contribute to pregnancy, even when examining various age groups. Lastly, there is no

significant difference between pregnancy outcomes when looking at race. These results

suggested that the type of adjunct acupuncture received is not important. The data hints

that non-White women should add adjunct acupuncture to their IVF protocols in an effort

to increase their own odds of achieving a positive pregnancy outcome. However more

racial diverse research is needed before that claim can be validated. The results of this

study offer additional information to women that allow for a more informed decision to

be made in regard to their fertility and the aid they seek when attempting to become

pregnant after an infertility diagnosis.

Following the careful analysis of the collected data the standardization of the

inclusion of adjunct acupuncture as a part of the IVF process is recommended. Although

there was no significant difference in pregnancy between the exposed and nonexposed

group, when compared with IVF alone, in the existing literature, the outcome of

pregnancy is increased from about 30% to approximately 50% when either form of

adjunct acupuncture is applied (exposed or nonexposed). More research is needed to

clarify which groups, if any, would receive the most benefit of adding adjunct

acupuncture. When women obtain guidance from a physician on the IVF procedure, a

discussion on the inclusion of adjunct acupuncture should be standard. Adjunct

acupuncture should be built into the IVF protocol for all women. The larger implications

for positive social change with the addition of adjunct acupuncture as a standard of care

would be an increase in pregnancy outcome compared with the previous IVF alone

protocol. Further studies with a larger targeted minority population might provide

evidence that suggest a reduction in the disproportionate success following the IVF

procedure that currently are present for non-White women.

Conclusions

Although the data showed there is no difference between pregnancy rates in the

exposed group and the nonexposed group, compared with prior published literature on

IVF alone, it can be inferred that the addition of adjunct acupuncture would increase odds

of pregnancy in women undergoing the IVF procedure. Additionally, the data analysis

encourages continued research on the addition of adjunct acupuncture for non-White

women as the IVF protocol with the addition of adjunct acupuncture decreases the racial

disparities of success. Further research is needed to determine if the addition of adjunct

acupuncture can help to reduce the decrease in odds of success among various age

groups. In summary, compared with existing literature, the data suggested adjunct acupuncture would likely increase pregnancy rates when compared with women who did not have adjunct acupuncture. The study data thereby suggested that the addition of adjunct acupuncture therapy could help to reduce the disproportionate success among various groups.

The implication for social change is a more personalized treatment plan, with better odds of a resulted pregnancy for those women whom have disproportionally been unsuccessful with IVF. Implementation of a practice that would add adjunct acupuncture as a standard of care recommendation during the IVF procedure may ultimately eliminate the variations of IVF success that are a result of racial differences. When compared with existing literature, the addition of adjunct acupuncture, as a standard of care, would also improve the odds of pregnancy for all women seeking IVF thereby reducing the number of attempts necessary to achieve pregnancy.

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Appendix: Data Collection Table

Subject ID IDs that start with **E** represent exposed cases IDs that start with **N** represent non-exposed cases (example E-001 = exposed case #1; N-001 = nonexposed case #1)	Age group **1**= 25-29 **2**= 3-34 **3**= 35-39 **4** = ≥40	Racal group **1**= American Indian or Alaska Native **2**= Asian **3**= Black or African American **4**= Native Hawaiian or Pacific Islander **5**= White	*Previous IVF cycle **Yes**/**NO**/**NA** *if available NA will be used for charts reviewed without comment about the number of previous IVF attempts	Pregnancy Outcome **Yes**/**No** Yes = + pregnancy No = - pregnancy
E-001				
N-001				

*This is a worksheet that was given to each clinic and was color coded and bolded for ease of use