ASSESSING THE LONG-TERM CARDIOVASCULAR OUTCOMES OF IN VITRO FERTILIZATION: A CROSS-SECTIONAL STUDY

A Research Grant Proposal

Presented to the faculty of the School of Nursing
California State University San Marcos

Submitted in partial satisfaction of
the requirements for the degree of

MASTER OF SCIENCE
in
Nursing
Family Nurse Practitioner

by
Shannon Michelle Doersam

SPRING 2016
CALIFORNIA STATE UNIVERSITY SAN MARCOS

PROJECT SIGNATURE PAGE

PROJECT SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

MASTER OF SCIENCE

IN

NURSING

PROJECT TITLE: Assessing the Long-Term Cardiovascular Outcomes of In Vitro Fertilization: A Cross-Sectional Study

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DATE OF SUCCESSFUL DEFENSE: 29 April 2016

THE PROJECT HAS BEEN ACCEPTED BY THE PROJECT COMMITTEE IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN NURSING.

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Abstract

of

ASSESSING THE LONG-TERM CARDIOVASCULAR OUTCOMES OF IN VITRO FERTILIZATION: A CROSS-SECTIONAL STUDY

by

Shannon Michelle Doersam

Now, more than ever, women are using assisted reproductive technology, specifically in vitro fertilization (IVF), to help them conceive (Sunderam et al., 2013). According to the Centers for Disease Control and Prevention survey in 2010, about 7.4 million of the 62 million women aged 15-44 years old (12%), had received infertility services at some point in their lives (2014). Nevertheless, IVF continues to be a controversial issue, as evidence remains inconclusive regarding the health outcomes for the offspring associated with this mode of conception. Consequently, women have difficulty making an educated decision concerning their chosen mode of conception. This study will examine the question: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process? The variables being measured include systolic blood pressure, diastolic blood pressure, high-density lipoprotein level, low-density lipoprotein level, and triglyceride level of these young adults.

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Date 29 APR 16
ACKNOWLEDGEMENTS

I would like to acknowledge my family and friends for their unconditional love and support over these past three years.

I would also like to acknowledge my committee chair members, Dr. JoAnn Daugherty and Dr. Denise Boren, for their continued guidance, support, and expertise along the way.
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CHAPTER I: INTRODUCTION

Background and Significance

The first infant in the United States conceived from assisted reproductive technology (ART) was born in 1981 (Sunderam et al., 2013). Thirty-five years later, the use of ART is now considered mainstream medical practice because of its effectiveness in overcoming infertility (Brison, Roberts, & Kimber, 2013). The number of ART procedures doubled nationwide between 1996 and 2010, while the number of infants born as a result of these procedures practically tripled (Sunderam et al., 2013). Moreover, about 1.5 million of these married women were considered to be infertile, meaning they were unable to get pregnant after one year of unprotected sexual intercourse (Centers for Disease Control and Prevention [CDC], 2014). With the development of IVF, the miracle of life has literally been brought to millions of families who otherwise would not have been able to conceive (Celermajer, 2012).

Worldwide, over five million babies have been born to date, using ART and the number is expected to increase exponentially in the next few decades, as the treatment continues to advance and more services become covered by health insurance (Hediger, Bell, Druschel, & Buck Louis, 2013). There were a total of 147,260 ART procedures reported to the CDC in 2010 that were performed in 442 fertility clinics nationwide (Sunderam et al., 2013). Currently, ART is responsible for about 1.4% of live births in the United States and more than 3% of live births in New York, New Jersey Massachusetts, District of Columbia, and Connecticut (Hediger et al., 2013).

Assisted reproductive technology includes intrauterine insemination (IUI), in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), surrogacy, or use of a gestational carrier. Nevertheless, about 99% of the ART cycles performed
use in vitro fertilization (Society for Assisted Reproductive Technology [SART], 2014). It is common knowledge that any type of incident or procedure that occurs around the time of conception and during fetal life has the potential to affect the growth, development, and health of an unborn child both in the short-term and the long-term time frame (Wilson, Fisher, Hammarberg, Amor, & Halliday, 2011). The manipulation of the gametes and embryos, that is the cornerstone of IVF, has been suspected to influence the vulnerable, developing child with questionable long-term consequences. According to Beydoun et al. (2010), IVF is not simply combining an egg and a sperm in a petri dish; rather there are several steps that are involved in the IVF process: hormonal stimulation, oocyte retrieval, fertilization, embryo culture, and intrauterine embryo transfer. There is great speculation that each of these steps can produce short and long-term health risks (Beydoun et al., 2010).

A major complication of IVF is a high multiple birth rate; about 47% compared to 3% with the general birth population, due to the transfer of multiple embryos (Sunderam et al., 2012). Babies conceived from multiple births (i.e. twins, triplets, etc.) related to IVF are more at risk of premature delivery (33% vs. 12%), low birth weights (32% vs. 8%), congenital abnormalities, and perinatal mortality when compared with the general birth population (Bergh & Wennerholm, 2012; Pandey, Shetty, Hamilton, Bhattacharya, & Maheshwari, 2012; Sunderam et al., 2012). In addition to risk factors that the IVF conceived child faces, the mother is also at risk of developing health related problems, as multiple births can lead to increased rates of cesarean deliveries and maternal disability (Sunderam et al., 2013). Further controversial complications among children conceived from IVF include an increase in cognitive impairments, cerebral palsy, autism, blood pressure, glucose levels, and generalized vascular abnormalities (Lu, Wang, & Jin, 2013). These documented health complications have contributed and will
continue to contribute to increasing healthcare costs for many Americans (Sunderam et al., 2013). For example, approximately 4% of all preterm births in 2010 were related to ART procedures nationwide, which accounted for a total economic burden far exceeding $1 billion (Sunderam et al., 2013). Despite these numbers, IVF continues to be the most widely used form of reproductive assistance nationwide with a limited amount of research into the health and long-term effects of this intervention.

In addition to the economic burden associated with outcomes related to IVF, the total cost of cardiovascular disease in the U.S. in 2010 was around $444 billion (CDC, 2010). Cardiovascular disease continues to be the number one cause of death in the U.S. with over 2,100 Americans dying each day (CDC, 2010). Therefore, not only is the information regarding IVF relevant, but so also is the information regarding the risk of cardiovascular disease among this specific population. This information is extremely relevant to nursing as patients and their families deserve the right to be informed of the possible and proven risk factors associated with in vitro fertilization.

Nurses, as well as advanced practice nurses (APN), play a vital role on the fertility specialty teams by providing necessary information, answering pertinent questions, running diagnostic tests, and listening to the concerns of the family. Additionally, APNs often provide counseling to patients of childbearing age as well as to families who are seeking further guidance regarding infertility services. They are responsible for explaining all the risks and benefits inherent in each mode of conception; therefore, APNs must continue to stay abreast on the most current technology and the most current research to provide the highest quality of patient care. As the field of fertility specialty continues to expand, so will the need for APNs and nurses, alike.
When women are contemplating which medical intervention would be best to help them conceive, the health of the future child should always be considered, as a great deal of time and money is invested into this decision. As the use of IVF becomes more widespread, knowing and understanding the short and long-term health outcomes in children conceived with this technology is crucial, so that women and their families who require medical and technological interventions to conceive understand the inherent risks and benefits (Eisenberg, 2012). Additionally, older individuals that were conceived through IVF are beginning to express their desire to understand whether the way they were conceived has health implications affecting and possibly influencing their futures (Wilson et al., 2011). To assist with providing this information, Congress passed the Fertility Clinic Success Rate and Certification Act in 1992 that mandated all fertility clinics in the U.S. performing ART procedures to annually report every ART procedure to the CDC (CDC, 2014). The Society for Assisted Reproductive Technology (SART), an affiliation of the American Society for Reproductive Medicine (ASRM), works in junction with the CDC to publish pregnancy success rates for ART in fertility clinics across the nation. These agencies have allowed researchers to find information regarding mothers and IVF babies in order to better investigate this mode of conception.

As the children conceived from IVF continue to age, so will the need to monitor the health outcomes associated with this ongoing process (Wilson et al., 2011). The American public deserves to have answers from evidence-based research regarding the inherent risks and benefits of this popular intervention that is used to overcome problems with infertility. Follow-up studies are limited to pregnancy complications and neonatal outcomes, instead of focusing efforts on the long-term health outcomes of the children as they progress into adulthood and reproductive-age (Miles et al., 2007).
Governmental agencies and research communities must continue to concentrate their efforts on studying this conventional treatment in order to determine the outcomes, all while keeping the public informed. A report from the President’s Council on Bioethics in 2004 indicated the need for long-term studies to assess health outcomes of IVF all while bringing attention to the decision-making process for parents and healthcare providers (NIH, 2014). This plea was followed by the Congressional report language for Fiscal Year 2008 that urged the National Institute of Child Health and Human Development (NICHD) to support the establishment of a multi-cohort study on ART to investigate long-term outcomes of this population (NIH, 2014). Currently, the National Institutes of Health (NIH) and the Department of Health and Human Services is looking to fulfill an exploratory/developmental research grant to fund a study researching the long-term outcomes of medically assisted reproduction (NIH, 2014).

The Problem

The problem remains that there is a limited amount of research on the long-term effects of IVF, specifically relating to the cardiovascular system, ultimately leaving women and their families with insufficient data on one of the biggest decisions of their lives. Consequently, it is imperative that this IVF population be studied. Following this need for further research, the main objective of this study is to perform a comprehensive assessment of IVF conceived young adults in an effort to identify any effects on the cardiovascular system that may benefit from further investigation.

Purpose of the Research

The purpose of this study is to determine whether or not young, college students (21-30 years old) born from in vitro fertilization are more at risk of developing cardiovascular disease
compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process.

**Research Question**

The question of this study asks, ‘Are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process?’

**Hypothesis**

The null hypothesis states that there will be no difference in the risk for developing cardiovascular disease between young, college students (21-30 years old) conceived from IVF versus young, college students (21-30 years old) naturally conceived. The alternative hypothesis states that young, college students (21-30 years old) born from IVF are more at risk of developing cardiovascular disease compared to young, college students (21-30 years old) spontaneously conceived.

**Research Variables**

The variables being measured include systolic blood pressure, diastolic blood pressure, high-density lipoprotein level, low-density lipoprotein level, and triglyceride level of these young adults. A multivariate analysis of variance (MANOVA) will be carried out to explore the relation between the method of conception and the cardiovascular measures.
CHAPTER II: LITERATURE REVIEW

Introduction

A series of literature searches of the PubMed, CINHAL, Cochrane, and Medline databases were conducted using the key words: in vitro fertilization, cardiovascular outcomes, long-term outcomes, neurological outcomes, IVF, assisted reproductive technology, growth and development, and long-term follow up. Only articles published between 2009 and 2014 and those written in English were explored, unless significant studies older than 2009 were necessary to offer additional information. When reviewing the literature, copious sources referred to the proven fact that babies born from assisted reproductive technology, specifically IVF, are more at risk of preterm birth, low birth weight, being small for gestational age, and perinatal mortality (Wilson et al., 2011). ART children were also found to require more medical treatment and be hospitalized more frequently when compared to babies spontaneously conceived (Wilson et al., 2011).

When reviewing the literature, three major topics were frequently discussed regarding the outcomes related to IVF: (1) growth and developmental outcomes; (2) neurodevelopmental outcomes; (3) cardiometabolic outcomes. Although not all of the reviewed literature is strictly related to the cardiovascular outcomes associated with IVF, it paints an excellent picture of the plethora of negative health outcomes that leaves even more questions to be answered regarding this mode of conception. In order to understand the importance of this proposed study, the additional health outcomes associated with IVF, beyond that of the cardiovascular system, must be explored to appreciate the need for further research of this population. Furthermore, the gap in the literature points to the fact that there is a limited amount of research investigating the long-
term cardiovascular outcomes among IVF individuals; hence, the main reason why this proposed study is so vitally important.

**Preliminary Studies**

**Neurodevelopmental Outcomes.** Hvidtjørn et al. (2009) published a systematic review and meta-analysis investigating the association between cerebral palsy (CP), autism spectrum disorders (ASD), and developmental delay and assisted conception. Forty-one studies were reviewed, two being case-control studies and the rest being cohort studies. Thirty of these investigated developmental delay on various standardized scales, nine assessed the risk of CP, and eight assessed the risk of ASD. Eight of the nine studies assessing CP were conducted in Scandinavia; nevertheless, all nine studies of singletons and multiples found that children born from IVF are at an increased risk of developing CP associated with preterm delivery compared with children spontaneously conceived (estimated odd ratio (OR), 2.18; 95% confidence interval (CI), 1.71-2.77). Due to the large size of the study cohorts, these studies offer persuasive evidence concerning the association between CP and IVF that is explained in part by an increased risk of premature delivery among babies conceived by IVF. Furthermore, there were inconclusive results from the eight ASD studies and the thirty studies on developmental delay (Hvidtjørn et al., 2009).

Another study by Zachor and Itzchak (2011) investigated the association between ART and ASD among a large Israeli population diagnosed with ASD using specific criteria based on standardized tests. They compared the prevalence of ART among a specific ASD population compared to the prevalence of ART among a large Israeli population using chi square goodness-of-fit tests. Their results indicated that 54 (10.7%) of the individuals diagnosed with ASD were conceived by ART. This rate of ART pregnancies (10.7%) was significantly higher than the
number of ART pregnancies (3.06%) in the large Israeli population ($\chi^2 = 93.2, p < .001$).

Nevertheless, the severity of the autism, adaptive skills, and developmental regression were not statistically significant in the IVF group compared to the spontaneously conceived group. Autism severity was analyzed using a one-way ANOVA, adaptive skills were evaluated using a one-way MANOVA, and the developmental regression was calculated with a Chi square analysis (Zachor & Itzchak, 2011). They concluded their study by reporting that assisted reproductive technology appears to be a substantial independent risk factor for ASD separate from other understood risk factors for ASD (i.e. maternal age, prematurity, low birth weight, etc.). Another study out of Southern Australia from 1986 to 2002 investigated a cohort of 308,974 births consisting of 6,163 IVF and intra-cytoplasmic sperm injection (ICSI) births (Davies et al., 2012). Results indicated that births from IVF and ICSI were associated with a significantly higher risk of any birth defect, when compared to births that did not involve assisted conception (unadjusted OR, 1.43; 95% CI, 1.26 to 1.62). This risk was weakened after adjusting for maternal age, parity, fetal gender, year of birth, maternal race/ethnicity, maternal smoking, socioeconomic status, and maternal and paternal occupation, to name just a few (adjusted OR, 1.24; 95% CI, 1.09 to 1.41). Despite the fact that most assisted conception births resulted in no birth defects, treatment with assisted reproductive technology was found to be associated with an increased risk of birth defects, including cerebral palsy, when compared to spontaneous conceptions (Davies, et al., 2012).

**Growth and Developmental Outcomes.** One study out of the Netherlands focused on assessing the pubertal development of children and adolescents born from IVF and compared them to children naturally conceived (Ceelen, van Weissenbruch, Vermeiden, van Leeuwen, & Delemarre-van de Waal, 2008b). Ceelen et al. (2008b) studied the bone age and sex hormone levels of 115 IVF-conceived boys and 115 IVF-conceived girls ranging in age from 8 to 18
years. The authors found that in the pubertal subpopulation (Tanner stage I), there was a higher bone age to chronological age (BA – CA) ratio and a larger BA to CA difference was found in the girls conceived from IVF compared to the girls naturally conceived (1.04 ± 0.07 versus 1.02 ± 0.08, \( P = 0.022 \)). Additionally, IVF-conceived girls were found to have significantly higher levels of dehydroepiandrosterone sulphate (DHEAS) and luteinizing hormone (LH) when compared to the control group of girls (2.5 versus 1.9 µmol/l, \( P = 0.017 \) and 1.5 versus 0.6 U/l, \( P = 0.031 \), respectively). There was no correlation found among the boys (Ceelen et al., 2008b).

Another study out of the Netherlands by many of the same authors focused on studying the body composition among 233 IVF singleton children born to subfertile parents ranging in age from 8 to 18 years old. They focused their efforts on determining whether or not postnatal body compositions were influenced by the method of conception. Using dual-energy x-ray absorptiometry (DXA) and anthropometry, measurements of bone mass, bone density, body fat mass, and lean mass were conducted in both the control group and the IVF group of children. Anthropometric measurements included height, weight, BMI, pubertal Tanner stage, and central fat measures in this study (Ceelen et al., 2007). Researchers found that peripheral adipose tissue mass assessed by skinfold measurements and DXA was significantly higher in IVF children compared to those spontaneously conceived (21.9 ± 10.4 versus 19.7 ± 8.9 mm, \( P = 0.014 \)). There was also a significant lower percentage of peripheral lean tissue among IVF children compared to those spontaneously conceived (69.0 ± 8.7 versus 70.5 ± 8.0, \( P = 0.023 \)). Although not statistically significant, skinfold measurements and DXA suggested that total body fat among IVF children was higher than control children (Ceelen et al., 2007). The authors concluded their study by referring to common knowledge that the amount of body fat is a major risk factor of
cardiovascular disease and that future research must be conducted regarding the long-term outcomes of IVF conception (Ceelen et al., 2007).

Cardiometabolic Outcomes. A follow-up study of the same 233 eight to eighteen year old IVF conceived participants in the Netherlands, discussed previously, was again conducted with the intention of assessing for blood pressure and body fat measures (Ceelen et al., 2009). Ceelen et al. (2009) investigated to see if there was an association between weight gain during infancy and early childhood in relation to body fat composition and blood pressure. As previously noted in the literature, babies conceived from IVF were found to have significantly lower birth weights and gestational ages compared to control groups. The post-natal growth of children was explored at three months, six months, and one year. Among the IVF children, the standard deviation scores of height ($P = 0.045$), weight ($P = 0.002$), and BMI ($P = 0.041$) were significantly lower at three months and the standard deviation score of weight was significantly lower at six months ($P = 0.027$). Results indicated that there was a significantly higher gain in height, weight, and BMI during late infancy (3 months – 1 year) in children conceived from IVF compared with the control group ($P = 0.013$, $P < 0.001$, $P = 0.029$, respectively). In IVF children only, systolic blood pressure and diastolic blood pressure were related to weight gain ($P = 0.014$, $P = 0.04$, respectively) during early childhood (1 - 3 years). Growth during late infancy was related to skinfold thickness in the control group only ($P = 0.003$). Additionally, skinfold thickness was related to growth during early childhood in both groups ($P = 0.003$ for IVF group; $P = 0.005$ for control group). Furthermore, rapid weight gain during early childhood appeared to be related to higher blood pressure readings at follow-up (independent of birth weight and gestational age) and that therefore was a better predictor of cardiovascular risk factors in IVF children only (Ceelen et al., 2009).
Researchers from the Netherlands produced yet another relevant study that was the first follow-up study to investigate cardiometabolic measures among 8 to 18 year old IVF singletons that compared these children to individuals that were spontaneously conceived (Ceelen, van Weissenbruch, Vermeiden, van Leeuwen, & Delemarre-van de Waal, 2008a). This follow-up study examined the blood pressure levels and fasting blood glucose levels in 225 children born from IVF and 225 control children that were matched via age (≤ 3 months difference) and gender to the IVF group. This study was paramount in determining that both systolic and diastolic blood pressures were found to be higher in children conceived from IVF compared to the control group (109 ± 11 versus 105 ± 10 mm Hg, \( P < 0.001 \) and 61 ± 7 versus 59 ± 7 mm Hg, \( P < 0.001 \), respectively). Additionally, the IVF children were found to be 2.1 times more likely to be in the highest systolic blood pressure quartile (OR = 2.1, 95% CI, 1.4 – 3.3) and 1.9 times more likely to be in the highest diastolic blood pressure quartile (OR = 1.9, 95% CI, 1.2 – 3.0) when compared to the control children. Furthermore, the children conceived from IVF had a greater sum of skinfolds (\( P = 0.04 \)) and higher fasting glucose levels (\( P = 0.005 \)) compared to the control group. IVF children were found to be 2.5 times more likely to be in the highest fasting glucose quartile (Ceelen et al., 2008a).

A logistic regression analysis was then carried out to control for confounding variables that included gender, current weight, birth weight, gestational age, parity, maternal smoking during pregnancy, parental education, parental age, maternal BMI, subfertility cause, and family history of disease (Ceelen et al., 2008a). According to Ceelen et al. (2008a), there was no significant difference between the IVF group and the control group in relation to height, weight, BMI, fasting insulin concentrations, and insulin resistance measures. The systolic blood pressure was found to be predominately affected by birth weight, gestational age, and sum of skinfolds;
whereas, the diastolic blood pressure was mostly affected by the parity of the mother (Ceelen et al., 2008a). After controlling for the relevant confounding factors with a multivariate regression analysis, the systolic blood pressure ($P = 0.003$), diastolic blood pressure ($P = 0.046$), and fasting glucose levels ($P = 0.02$) among IVF children remained significantly higher compared to the control group (Ceelen et al., 2008a). Although there was only a 3 to 4 mm Hg increase in the systolic blood pressure and a 1 to 2 mm Hg increase in the diastolic blood pressure among the IVF group, these are still considered to have a major impact on the individual’s health (Ceelen et al., 2008a). According to Ceelen et al. (2008a), there is a remarkable increase in the risk of developing cardiovascular disease with only a slight increase in blood pressure. For example, medical research demonstrates that by lowering an adult’s systolic blood pressure by 2 mm Hg, they then have an 8% less chance of experiencing a cerebral vascular accident (as cited in Ceelen et al., 2008a).

While the results of this study could not be explained by the previously discussed current risk indicators, early life factors, and parental characteristics, additional research must be conducted relating to cardiovascular risk among IVF offspring before definite conclusions can be made (Ceelen et al., 2008a). The findings of this study further emphasize the importance of continuing to monitor the postnatal development of IVF children worldwide with regard to the development of short and long-term cardiovascular outcomes from this common medical practice (Ceelen et al., 2008a).

**Conceptual Framework**

The multi-dimensional conceptual framework utilized in this grant proposal was developed by a group of professors and researchers at the University of London that critiqued and thoroughly evaluated different concepts relating to research agenda setting and informed
decision-making before developing a conceptual framework of their own. Oliver and colleagues proposed the Public Involvement Framework that focuses its efforts on analyzing public involvement in the research of health services (Oliver et al., 2008). This original conceptual framework takes into account the people initiating the involvement, the people that are actually involved, the degree of public involvement, the medium of exchange, and the decision-making methods (Oliver et al., 2008). This Public Involvement Framework discusses the fact that the American public wants to be informed of all the latest research regarding a specific health service in order to help them make their best educated decision regarding using the service or not. By having the research findings and the documented outcomes associated with the service be accessible in the public domain, the health service is then held accountable for all of its documented findings. People are primarily interested in the healthcare that pertains to their own health and the health of their family. The individuals that are users of the service or product are labeled many things including ‘users’, ‘patients’, ‘consumers’, ‘citizens’, and ‘lay people’ (Oliver et al., 2008). When a consumer is able to make his or her own choice regarding the use of a service based on documented research regarding the service, this is termed consumerism. Oliver et al. (2008) built this conceptual framework to explore how the involvement of the general public (not researchers or service professionals) has and will continue to guide what research is conducted and how it is conducted.

The anticipated results of this study will hopefully better inform the public regarding the risks and benefits inherent in their decisions regarding assisted reproductive technology. This study is of high significance because it will provide access to documented long-term outcomes related to IVF. The results will provide the necessary and evidence-based information to people
who were conceived by this method, as well as to women and their families who are trying to make a decision that will ultimately change their lives forever.
CHAPTER III: METHODOLOGY

Research Design and Methodology

As previously discussed, in vitro fertilization has revolutionized the field of human reproduction for the past three decades; nevertheless, research continues to demonstrate that the long-term effects of this reproductive technology are limited, conflicting, and controversial (CDC, 2014). The manipulation of the gametes and embryos that is the cornerstone of IVF has been suggested to influence the vulnerable, developing child with questionable long-term consequences (Ceelen et al., 2007). Consequently, there have been multiple health problems documented in the research associated with IVF. It is imperative that this specific population continues to be studied, as the problem remains that the current amount of limited data is not sufficient to provide women and their families with the most current research regarding IVF to help them make the most educated decision regarding their mode of conception.

The purpose of this study is to determine whether or not individuals born from in vitro fertilization are more at risk of developing cardiovascular disease compared to individuals spontaneously conceived. College students, ranging in age from 21 to 30 years old, who are attending universities in San Diego County, will be recruited into either the IVF group or the control group. This is the target population because there have been no studies beyond the age of 18 in the literature looking at the long-term effects of IVF related to cardiovascular disease. This cross-sectional study design will use the Public Involvement Framework that was proposed by Oliver et al. in 2008. As discussed in the conceptual framework, this information is extremely relevant to nursing as patients and their families deserve the right to be informed of the possible and proven risk factors associated with in vitro fertilization.
IVF and naturally conceived subjects will be recruited from three different universities in San Diego County. For each participating IVF adult, there will be one control adult of the same gender, similar age (<3 months age difference), and similar physical activity level (i.e. light workout <2x/week, moderate workout 3-4x/week, or heavy workout>5x/week), who was naturally conceived. By pair matching the participants’ age, gender, and physical activity level in both groups, this will help to control for threats to internal validity. The variables measured will be systolic blood pressure, diastolic blood pressure, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides of these young adults in both groups. These variables were chosen based on the significant results in previous research studies of adolescents, as well as the fact that they are proven risk factors associated with cardiovascular disease. In summary, the research question being addressed asks: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process?

**Hypothesis**

The null hypothesis states that there will be no difference in the risk for developing cardiovascular disease between young, college students (21-30 years old) conceived from IVF versus young, college adults (21-30 years old) naturally conceived. The alternative hypothesis states that young, college students (21-30 years old) born from IVF are more at risk of developing cardiovascular disease compared to young, college students (21-30 years old) spontaneously conceived.
**Variables Defined**

The independent variable for this study is method of conception. This is a dichotomous variable with two groups: natural or spontaneous conception (NC) and in vitro fertilization (IVF). Additionally, there are five ratio-scale variables that will be assessed in this study and they must therefore be defined in order to understand the proposed study: systolic blood pressure, diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. Systolic blood pressure is the top number of the blood pressure reading and is defined as the pressure in the arteries when the heart muscle contracts (American Heart Association [AHA], 2014a). Diastolic blood pressure is the bottom number of the blood pressure reading and is defined as the pressure in the arteries when the heart muscle is resting and refilling (AHA, 2014a). According to the AHA, for individuals 20 years and older, a normal systolic blood pressure is less than 120 mm Hg and a normal diastolic blood pressure is less than 80 mm Hg. Prehypertension is a systolic blood pressure of 120-139 mm Hg and a diastolic blood pressure of 80-89 mm Hg. Hypertension stage I is a systolic blood pressure 140-159 mm Hg and a diastolic blood pressure of 90-99 mm Hg. Hypertension stage II is a systolic blood pressure of 160 mm Hg or higher and a diastolic blood pressure of 100 mm Hg or higher. A hypertensive crisis consists of a systolic blood pressure greater than 180 mm Hg and a diastolic blood pressure greater than 110 mm Hg. LDL is the main source of cholesterol buildup and blockage in the arteries and is considered to be the ‘bad’ cholesterol (AHA, 2014b). A LDL level of less than 100 mg/dL (or a level less than 70 mg/dL for persons with a history of heart disease or those at very high risk), is considered optimal (MedlinePlus, 2011). HDL helps to remove cholesterol from your arteries and is considered to be the ‘good’ cholesterol (AHA, 2014b). According to MedlinePlus (2011), men should have a HDL level above 40 mg/dL and
women should have one above 50 mg/dL. Triglycerides are another type of fat being assessed and high levels are associated with atherosclerosis (AHA, 2014b). The normal range for this test is less than 150 mg/dL (MedlinePlus, 2013).

**Population and Sample**

The target population for this study includes college students attending universities in San Diego County who were conceived from IVF and were born between 1984 and 1993. There is no documentation of the success rates of IVF during this time period; however, the first report by the CDC was released in December of 1997 (CDC, 1997). This document, entitled the *1995 Assisted Reproductive Technology Success Rates Report*, indicates that there were approximately 164 IVF children born in San Diego County in 1995 (CDC, 1997). In order to estimate the target population over 10 years (1984-1993), 164 must be multiplied by 10 years to equal 1,640. Therefore, the total approximation of the target population from San Diego County only is 1,640. Subjects who were born outside San Diego County but attend college in San Diego are also eligible.

The participants for this study will be recruited using convenience sampling with techniques based on the literature review (Polit & Beck, 2012). The required sample size was calculated using the software program G-power. A G-power analysis was performed for the MANOVA, using an F-test (see Appendix A for complete analysis). The sample size according to the F-test was calculated to detect a medium strength main effect size of 0.50, an alpha level of 0.05 with a power of .80. The effect size is based on previous studies of the long-term effects of hormone stimulation and IVF. The total sample size according to this analysis was 32. When adding 20% for loss factors, the desired sample size is 38 participants (32 x .2 = 6.4; 6.4 + 32 = 38.4 or 38). It is important to assess for loss factors to account for individuals that may not
follow up with the study if they have to seek additional help from family members to complete the demographic questionnaire. Furthermore, due to the fact that we will be controlling the enrollment by matching subjects, 19 of the 38 participants will be conceived from IVF and 19 will be naturally conceived.

**Inclusion criteria.** Participants of the case group must be singletons conceived from IVF, born in the United States between 1984 and 1993, living in San Diego County, and speak English. Participants of the control group must follow all of the same inclusion criteria as the case group except for the fact that they were naturally conceived.

**Exclusion criteria.** Potential participants in both the IVF and NC groups will be excluded if they currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication.

**Data Collection Process**

The recruitment of subjects will occur on three large college campuses in San Diego to reach the most individuals between the ages of 21 and 30 years old (i.e. undergraduate and graduate students). The three campuses will include California State University San Marcos, San Diego State University, and the University of California San Diego. Approval from the Institutional Review Boards (IRB) will be obtained from all three colleges prior to any type of recruitment. School email addresses for potential candidates will be acquired from the registrar’s office on each of the campuses. A registered email of invitation will be sent out to all students ranging in age from 21 to 30 years old about two months before arriving on campus to recruit
(see Appendix B). The email will give a detailed explanation of the purpose of the study, what the study entails, the risks and benefits associated with the study, information regarding the $25 Visa gift card that will be given as an incentive for participating in the study, and will conclude by asking for participation in the study. Due to the busy nature of undergraduate and graduate lifestyles, a follow-up email will be sent out one month before data collection begins and a final email will go out one week before arriving on campus to recruit. The recruitment process will take place in a previously reserved conference room at each university. The specific location will be included in the final email that goes out one week before arriving on campus so potential participants are aware of our location. Participants will be consented if they agree to participate in the study. For each participating IVF young adult, we will search for one control adult of the same gender, similar age (≤3 months age difference), and similar physical activity level (light, moderate heavy) that was naturally conceived. In the case that an approached adult does not want to participate, the control recruitment process will be repeated until an appropriate control adult is found that is willing to participate in the study. Once the participants agree to participate in the study, they will be given a demographic questionnaire to fill out regarding some current risk indicators, early life factors, and parental characteristics that will help to evaluate the results of the study (see Appendix C for complete questionnaire). The questionnaires will be color coded to determine the mode of conception of each participating individual (i.e. white paper if naturally conceived, yellow paper if conceived by IVF). Furthermore, to obtain face validity, a group of 21-30 year old bachelor prepared registered nurses who work on an open-heart surgery floor at a local hospital reviewed the demographic questionnaire prior to the distribution period. Unanimously, they confirmed that the questions were straightforward and that they understood
what was being asked. They also verified that the questions would collect the appropriate data being investigated, ultimately providing content validity.

If the young adult is not able to complete the questionnaire, they will be asked to call their family to obtain this information. If this is still not feasible, they will be asked for their telephone numbers and will be notified that a representative of the study will follow-up with a phone call to obtain this information. They will then be asked to go to their student health clinic on campus to have their blood pressure taken and their blood drawn if they have been fasting for the past eight to twelve hours as indicated in the emails. If we have not met the quota of 38 participants and they have not been fasting, they will be asked to do so overnight and return the following morning to the student health clinic on campus to have their blood pressure taken and their blood drawn. The same nurse will obtain blood pressure and draw the participant’s blood at each of the three campuses as data collection for each university will occur on separate days. The nurse will be oriented to protocol and method for obtaining blood pressure prior to data collection. The nurse will not be informed of the mode of conception of each individual in order to decrease any misclassification bias.

Measurement Methods

After confirming that the participant has been fasting for eight to twelve hours, they will be asked to arrive at their student healthcare clinic to have their blood pressure taken before their blood sample is obtained. The previously trained nurse will take the blood pressure of each participating individual. When measuring the systolic and diastolic blood pressure, the auscultation method will be used, as this is the gold standard for measuring blood pressure by the Heart, Lung and Blood Institute of the NIH. With the World Health Organization committing to removing all mercury-containing devices from healthcare settings in 2005, an aneroid
sphygmomanometer will be used instead, as this device has proven to be equally or more accurate than the mercury sphygmomanometers (Buchanan, 2009). The sphygmomanometer will be checked and calibrated by a qualified technician to ensure accurate readings prior to examination. With the proper technical maintenance, the sensitivity and specificity of this device is identical to the standard mercury manometer device (Tholl, Forstner, & Anlauf, 2004).

Participants will be asked to sit quietly for at least five minutes in a chair, with both feet on the floor and the arm supported at the heart level (National Heart, Lung and Blood Institute, 2004). After confirming that the participant has not exercised, smoked, or had caffeine 30 minutes prior to the assessment, the blood pressure will be measured three times on the non-dominant arm, with three-minute intervals in between each assessment. The nurse will verify that they are using the appropriate size cuff for each participant, will position the cuff 2-3 cm above the antecubital fossa, and will position the central portion of the rubber bladder of the stethoscope on the brachial artery. The mean of the three readings will be used in analysis.

The participants will then have their blood drawn after the allotted fasting period. The same nurse, at each location, will draw blood samples for each participant. The nurse will be provided sufficient training in the safe operation and maintenance of the point-of-care testing (POCT) equipment. The labs to be drawn include HDL, LDL, and triglycerides of each participant. Once the blood is drawn, the results of each participant will be reviewed for analysis. The Alere Cholestech LDX® Analyzer System will be the machine used to gather this information. This POCT provides accurate data as Alere participates in the only available CDC standardization program that follows the National Cholesterol Education Program performance goals, the Cholesterol Reference Method Laboratory Network (CRMLN), and Lipid Standardization Program certifications. For example, one study including 53 donors had finger
stick specimens taken and were evaluated using four Alere Cholestech LDX® analyzers. The same participants had venous specimens sent to a commercial and CRMLN laboratories and results indicated that the LDL cholesterol assessment was in close agreement between the POC testing (93.3%) and the laboratory testing (93.6%) (Alere, 2014; Carey, Markham, Gaffney, Boran, & Maher, 2006). Additionally, another study confirmed that the Alere Cholestech LDX® Analyzer System was an adequate POC testing machine for the National Health Service Health Check (Jain et al., 2011). Jain et al. (2011) explained multiple advantages of point-of-care testing including convenience for patients, less blood quantities needed, eliminating the possibility of misplacing/mislabeling a blood specimen that is sent to the laboratory, and prompt results allowing for immediate feedback and prompt treatment.

There will be a master logbook where patient identification will be kept private in a lock box. Each participant will be correlated with a case identification number (see Appendix D for data collection worksheet). Therefore, after a participant fills out the questionnaire they will be matched with a case identification number that will be their identification as they continue to have their blood pressure and blood work completed.

The master logbook will be locked away and stored in a lock box and placed on the top shelf of a locked cabinet (completely out of site to the public), inside each of the student health centers. The research assistant and myself will be the only two individuals to have access to the data. The access will be limited to us as we will be the only ones with a key. The data will be retained for one year after the project is completed. The paper records will be shredded and the digital files will be erased.

**Statistical Analysis**
Statistical analysis will be completed using the SPSS (Statistical Package for the Social Sciences) program. A multivariate analysis of variance (f-test) will be carried out to explore the relation between the method of conception and cardiovascular measures. The alpha level is .05. Any p value that is greater than .05 will be considered non-significant. Demographic data will be reported for current risk factors (i.e. current weight, height, body mass index, physical activity level), early life factors (i.e. maternal smoking during pregnancy, birth weight, gestational age) and parental factors (i.e. family history of hypertension, family history of cardiovascular disease). The demographic variables of weight, height, body mass index, physical activity level, birth weight, and gestational age are all ratio scale variables. The yes or no answers regarding maternal smoking during pregnancy, family history of hypertension, and family history of cardiovascular disease make all these variables nominal measurements.

**Limitations and Biases**

The limitations of the proposed sample’s generalizability allow the results of this study to only be generalized among 21 to 30 year olds born from IVF attending universities in San Diego County. A potential bias in all cross-sectional studies is that of participation bias wherein the number of non-responders can result in bias of the measure of outcome (Polit & Beck, 2012). The follow-up reminder emails will be sent out prior to recruitment to help with this bias as research demonstrates they have proven to be effective in achieving higher response rates (Polit & Beck, 2012).

The physical appearance and simplicity of the demographic questionnaire was designed to appeal to busy college and graduate school students that do not have time for lengthy questions. Additionally, 21-30 year old bachelor prepared registered nurses who work on an open-heart surgery floor at a local hospital reviewed the questionnaire. Unanimously, they
verified that the questions that were being asked would collect the appropriate data being investigated, ultimately providing content validity.

In order to prevent any misclassification bias, the nurse obtaining the blood pressures at each student health center will not be informed of the mode of conception of each participating subject to prevent any skewed results. As far as controlling for threats of internal validity, the participating individuals in both groups will be matched based on age, gender, and level of physical activity, a term referred to as pair matching (Polit & Beck, 2012). This will help to control for selection bias. Additionally, the threat of temporal ambiguity is always possible in a cross-sectional study as it may be unclear whether the independent variable preceded the dependent variable or vice versa (Polit & Beck, 2012).

**Ethical Considerations**

After providing full disclosure to all participating subjects, informed consent will be obtained and IRB approval will be granted from all three universities prior to implementation of the study. Additionally, the lab records and the demographic questionnaires will be confidentially stored in a lock box at each of the student health centers for confidentiality purposes. Furthermore, the $25 Visa gift card will be offered to all participating subjects to reduce chances of attrition, especially when some participating subjects are unable to answer all the questions from the demographic questionnaire and must seek additional help from family members prior to completing the study. Lastly, if any individual throughout the course of the study is found to have any concerning results including high blood pressure or elevated cholesterol levels, they will immediately be contacted and told to see their primary care provider for follow-up.
CHAPTER IV: GRANT ELEMENTS

Selected Grant

The National Institutes of Health (NIH) and the Department of Health and Human Services Grant: Long-Term Outcomes of Medically Assisted Reproduction (NIH, 2014). This grant is seeking to analyze the long-term health outcomes of children born from assisted reproductive technology. The goal of this study is to provide women and their families with the most current and up-to-date information regarding the inherent risks and benefits of these commonplace advancements in today’s society. Since the purpose of this research is to investigate and determine the long-term consequences of assisted reproductive technology, including in vitro fertilization, this selected grant is the most logical choice to apply for funding.

Funding is up to $200,000.00 in one single year. The proposed study will take place over one academic calendar year, totaling $199,558.00

Detailed Budget

The primary researcher, Shannon Michelle Doersam, is a registered nurse of six years in San Diego County. She works at a local hospital on the open-heart surgery floor where she has gained a vast amount of knowledge in the field of cardiology. She assesses, treats, and educates individual patients on their cardiovascular health on a daily basis. Additionally, she is currently in the family nurse practitioner program at California State University San Marcos where she engages in assessing, diagnosing, and treating individuals of all ages. She has worked with neonates both inside and outside of the hospital as well as working with patients that are currently utilizing IVF treatments. Shannon will be overseeing the entire study and will assist with obtaining IRB approval from each university, budget analysis, sending out registered emails
of invitation, data collection, and data analysis. She will devote 25% of her time to the grant. Shannon will be provided $75,000.00 for the entire grant proposal.

The research assistant will ideally be master’s prepared with at least three years experience as a research assistant in adult healthcare. He/she will be in charge of the recruitment of students from all three universities. He/she will be responsible for sending out all email notifications to prospective students, verifying the conference rooms are reserved at each location prior to recruitment, collecting consent forms and demographic questionnaires, and verifying that all documents are complete. Additionally, he/she will be responsible for providing participants with the $25 Visa gift card after verifying that all steps of the study have been completed. As recruitment time subsides, the research assistant will help with data entry into SPSS>

The registered nurse will ideally be bachelor’s prepared with at least two years of experience as a registered nurse in adult healthcare. He/she will be responsible for obtaining the blood pressure of all participants at each of the three universities. He/she will be oriented on the protocol and method for obtaining blood pressure prior to data collection. Additionally, he/she will obtain a blood sample from each participant following the appropriate protocol of the Alere Cholestech LDX® Analyzer System. The registered nurse will devote 25% of his/her time to the grant. He/she will be provided $25,000.00 for the entire grant proposal.

JoAnn Daugherty, Ph. D., RN, CNL, will serve as the project committee chairman and statistical consultant for this grant proposal. Dr. Daugherty is a faculty member at California State University San Marcos with over 20 years experience in cardiovascular nursing. She has worked with patients who have hypertension and hyperlipidemia including outpatient testing for
these disorders. Dr. Daugherty will assist with database design in SPSS software and will aid with analysis and interpretation of the quantitative data. She will provide 50 hours of assistance at $100/hr for a total of $5,000.00 for the entire grant proposal.

The major piece of equipment required to conduct this study is the Alere Cholestech LDX® Analyzer System. The machine is vital in obtaining the LDL, HDL, and triglyceride levels of each participant. Additionally, a professional aneroid sphygmomanometer will need to be purchased to conduct accurate blood pressure readings. These two pieces of equipment can be purchased for approximately $2,821.00.

Office/computer supplies required to conduct the study include a laptop computer, printer, SPSS IBM 21.0, copier expenses, pens, and copy paper. A laptop computer will allow all the data collection and analysis to take place on the SPSS IBM 21.0 software that will be used in analysis. A printer, copier expenses including ink, and copy paper will be required to print all of the consent forms and the demographic questionnaires as well as having pens available for participants to fill out the forms. Data analysis equipment/supplies required for this study include test cassettes for the Alere machine, Alere lancets, capillary tubes and plungers, sharps container, alcohol pads, bandages, gauze pads, biohazard container, gloves, and a lock box. All of these products will allow for the blood testing of the LDL, HDL and triglyceride levels of each participant. In addition, a secure lock box will be required to store all confidential documents. All of these supplies will cost approximately $3,462.00.

Travel expenses include providing reimbursement for all driving costs. Depending on the number of eligible participants at each university on the first day of recruitment, there will be a minimum of six days traveling (two days at each university) with a maximum of twelve days
traveling (four days at each university if the appropriate number of eligible participants is not met on the first day). Travel costs will be approximately $2,400.00.

Three additional expenses including conference costs, student health center costs, and participant incentive costs must be factored in to the total budget. First, the research results will be presented at three separate conferences across the United States. The 73rd American Society for Reproductive Medicine (ASRM) annual conference will be held in San Antonio, Texas, from October 28th to November 1st, 2017. The estimated registration fee is $575.00. Round-trip airfare will be approximately $550.00. Hotel fees for a four-night stay will be approximately $600.00. A rental car for five days will total $250.00. Estimated food cost will be about $250.00 for five days. Total cost is estimated at $2,225.00. The American Association of Nurse Practitioners (AANP) annual national conference will be held in Philadelphia, Pennsylvania, from June 20-25, 2017. The estimated registration fee is $705.00. Round-trip airfare will be approximately $650.00. Hotel fees for a five-night stay will be approximately $750.00. A rental car for six days will total $300.00. Estimated food cost will be about $300.00 for six days. Total cost is estimated at $2,705.00. The Society for Research in Child Development (SRCD) biennial conference will be held in Baltimore, Maryland, from March 21-23, 2019. The estimated registration fee is $695.00. Round-trip airfare will be approximately $700.00. Hotel fees for a two-night stay will be approximately $300.00. A rental car for three days will total $150.00. Estimated food cost will be about $150.00 for three days. Total cost is estimated at $1,995.00. Therefore, the total conference costs will be approximately $6,925.00.

Next, each university will be reimbursed for allowing a small area of their student health center to be devoted to this study for data collection. Each university will be given $1,000.00, for a total of $3,000.00. Another expense involves that of providing incentive to participants for
completing the entire study. A $25.00 Visa gift card will be provided to all 38 participants after completion of the study for a total of $950.00 ($25 x 38 = $950).

The table below shows a detailed budget for the entire proposed study.

<table>
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<th>NAME</th>
<th>ROLE ON PROJECT</th>
<th>Cal. Mnths</th>
<th>Acad. Mnths</th>
<th>Summer Mnths</th>
<th>INST.BASE SALARY</th>
<th>SALARY REQUESTED</th>
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<td>25,000</td>
</tr>
</tbody>
</table>

SUBTOTALS 175,000

CONSULTANT COSTS
Dr. JoAnn Daugherty, Ph. D., RN, CNL; statistical consultant; provide 50 hours/$100/hour 5,000

EQUIPMENT (Itemize)
Alere Cholestech LDX® Analyzer System 2,821
Professional Aneroid Sphygmomanometer

SUPPLIES (Itemize by category)
Office/Computer Supplies: Laptop computer, printer, SPSS IBM 21.0, copier expenses, general office supplies, copy paper. Data Analysis Equipment/Supplies: Test cassettes for the Alere machine, capillary tube & plungers, sharps container, Alere lancets, alcohol pads, bandages, gauze pads, biohazard container, gloves, lock box. 3,462

TRAVEL
Driving costs to 3 different universities. Minimum 6 days, maximum 12 days of driving 2,400

INPATIENT CARE COSTS 0
OUTPATIENT CARE COSTS 0

ALTERATIONS AND RENOVATIONS (Itemize by category) 0
Timeline

The proposed study will take place over one academic calendar year in order to reach the most eligible number of students. Eligible participants may be studying abroad one semester or transferring to the university in the spring semester; therefore, recruitment needs to occur both in the fall and spring terms. After obtaining IRB approval from all three universities in Fall of 2016, recruitment for participants will begin immediately. Two months before the anticipated date of recruitment at each university, a registered email of invitation will be sent out to all eligible participants at each university. Another email will be sent out one month before recruitment and the last email will go out one week before recruitment. Research will be conducted at California State University San Marcos on November 28, 2016, and February 14, 2017, from 07:00 to 21:00. Research will then be conducted at San Diego State University on December 1, 2016, and February 16, 2017, from 07:00 to 21:00. Lastly, research will be conducted at the University of California San Diego on December 5, 2016, and February 20, 2017, from 07:00 to 21:00. The study will take place over the course of one academic calendar year (Fall 2016 through Spring 2017).

Dissemination Plan
The results of this study will be located in California State University San Marcos’ library archives. Additionally, the results of this study will be sent to the Department of Health and Human Services, the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute, the Society for Assisted Reproductive Technology, and the Centers for Disease Control and Prevention (CDC). The manuscript will be submitted for publication to the Journal of the American Medical Association (JAMA). The study will be presented at three conferences across the nation: the American Society for Reproductive Medicine (ASRM) annual conference in October 2017, the American Association of Nurse Practitioners (AANP) annual conference in June 2017, and the Society for Research in Child Development (SRCD) biennial conference in March 2019. Furthermore, there will be a literature review manuscript submitted to the Journal of Nurse Practitioners or the Journal of the American Association of Nurse Practitioners summarizing the results of the study as well as studies discussed in the literature review section. These articles will provide information on the most current research regarding the long-term cardiovascular outcomes associated with in vitro fertilization. This newfound knowledge will allow nurses, as well as advanced practice nurses, to educate women and their families on the latest research regarding this chosen mode of conception.
References


after assisted conception: a systematic review and meta-analysis. *Archives of Pediatrics & Adolescent Medicine, 163*(1), 72–83.


doi:10.1016/j.ridd.2011.05.007
Appendix A

**G-Power Analysis: Multivariate Analysis of Variance (MANOVA)**

![G-Power Analysis screenshot](image)

### Test family
- F tests

### Statistical test
- MANOVA: Global effects

### Type of power analysis
- A priori: Compute required sample size – given α, power, and effect size

### Input parameters
- **Determine**
  - Effect size η²(V) = 0.5
  - α err prob = 0.05
  - Power (1-β err prob) = 0.8
  - Number of groups = 2
  - Response variables = 5

### Output parameters
- Noncentrality parameter λ = 16.000000
- Critical F = 2.5867901
- Numerator df = 5.000000
- Denominator df = 26.000000
- Total sample size = 32
- Actual power = 0.8057992
- Pillai V = 0.3333333
Appendix B

Recruitment Emails

1st Email to Students (sent out two months before arriving on campus to conduct study):

Research Study: Assessing the Long Term Cardiovascular Effects of In Vitro Fertilization

Hello Student of [insert university name here],

Come be a part of an important and exciting research study that will be taking place at [insert name of university here] on [insert date here]. If you are between the ages of 21 and 30 years old you may be eligible to participate. This purpose of this study is to answer the question: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process? The study will attempt to answer this question by comparing the systolic blood pressures, diastolic blood pressures, high-density lipoprotein levels, low-density lipoprotein levels, and triglyceride levels among those conceived from IVF compared to those naturally conceived. You may be eligible for this study if you were born in the United States between 1984 and 1993, live in San Diego County, and speak English. Unfortunately, you will not be allowed to participate in this study if you currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication.

If you are eligible and decide to participate in this study you will be asked to arrive the morning of the study fasting. This means that you will not be allowed to have eaten or drank anything since midnight the night before the study. You will then be given information regarding the study including the risks and benefits of participating and will be asked to sign a consent form. Following this, you will be given a demographic questionnaire to fill out regarding some information about yourself and your family. Once the questionnaire is completely filled out, you will be asked to go to the student health center on campus where you will have your blood pressure taken and your blood drawn. You will receive a $25 Visa gift card for participating in the study.

Please understand that this email is not telling you that you have to join this study. It is your decision. Your participation is completely voluntary. Whether or not you participate in this study will have no effect on your relationship with the university. We look forward to speaking with those who may be interested in participating in this study. Please feel free to contact me with any questions you may have using the contact information provided below.

Sincerely,
2nd & 3rd Emails to Students (sent out 1 month before and 1 week before arriving on campus to conduct study):

Research Study: Assessing the Long Term Cardiovascular Effects of In Vitro Fertilization

Hello Student of [insert university name here],

This is a reminder email that we will be at [insert name of university here] in the [exact conference room location] on [insert date here] conducting an important and exciting research study and we would love your participation! If you plan on participating please remember to show up fasting on the morning of the study. We have attached the previous email that was sent out if you need a reminder of what this study is all about. Please contact me if you have any questions. We look forward to your participation.

Sincerely,

Shannon M. Doersam
California State University San Marcos
Family Nurse Practitioner Student
Doers001@cougars.csusm.edu
(949) 422-9519

(PREVIOUS EMAIL)

Come be a part of an important and exciting research study that will be taking place at [insert name of university] on [insert date here]. If you are between the ages of 21 and 30 years old you may be eligible to participate. This purpose of this study is to answer the question: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process? The study will attempt to answer this question by comparing the systolic blood pressures, diastolic blood pressures, high-density lipoprotein levels, low-density lipoprotein levels, and triglyceride levels among those conceived from IVF compared to those naturally conceived. You may be eligible for this study if you were born in the United States between 1984 and 1993, live in San Diego County, and speak English. Unfortunately, you will not be allowed to participate in this study if you currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a
congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication.

If you are eligible and decide to participate in this study you will be asked to arrive the morning of the study fasting. This means that you will not be allowed to have eaten or drank anything since midnight the night before the study. You will then be given information regarding the study including the risks and benefits of participating and will be asked to sign a consent form. Following this, you will be given a demographic questionnaire to fill out regarding some information about yourself and your family. Once the questionnaire is completely filled out, you will be asked to go to the student health center on campus where you will have your blood pressure taken and your blood drawn. You will receive a $25 Visa gift card for participating in the study.

Please understand that this email is not telling you that you have to join this study. It is your decision. Your participation is completely voluntary. Whether or not you participate in this study will have no effect on your relationship with the university. We look forward to speaking with those who may be interested in participating in this study. Please feel free to contact me with any questions you may have using the contact information provided below.
Appendix C

Demographic Questionnaire

Questionnaire

Thank you so much for participating in this study to determine whether or not young adults born from in vitro fertilization (IVF) are more at risk of developing cardiovascular disease compared to young adults spontaneously conceived.

**Please fill out the information to the best of your ability**

1. Gender:  Male / Female / Transgender  Age:  ___________

2. Weight:  ___________  Height:  ___________

3. How many days a week do you workout?  0-2 days/week  3-4 days/week  5+ days/week

4. How much did you weigh when you were born (birth weight)?  ________________

5. How far along was your mother when she delivered you (gestational age)?  ______

6. Did your mother smoke during her pregnancy with you?  Yes  or  No

7. Do you have a family history (parents, grandparents) of hypertension?  Yes  or  No

8. Do you have a family history (parents, grandparents) of cardiovascular disease?  Yes  or  No

Thank you again for your participation.
Appendix D

Data Collection

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<th>Family History of Hypertension</th>
<th>Family History of Cardiovascular Disease</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
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Assessing the Long-Term Cardiovascular Outcomes of In Vitro Fertilization: A Cross-Sectional Study

Dear student,

My name is Shannon Doersam and I am a family nurse practitioner student in the School of Nursing at California State University San Marcos. You are invited to participate in a research study assessing the long-term cardiovascular outcomes among individuals born from in vitro fertilization compared to individuals naturally conceived. You were selected as a possible participant because you are a young, college student, between the age of 21 and 30 years old. Please read this form carefully and ask any questions you may have before agreeing to be in the study. You must be between the ages of 21 and 30 to participate in the study.

STUDY PURPOSE:
The purpose of this study is to determine whether or not young, college students (21-30 years old) born from in vitro fertilization are more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process.

NUMBER OF PARTICIPANTS:
If you agree to participate, you will be one of thirty-eight participants who will be participating in this research. The thirty-eight participants will be separated into two groups of nineteen. Nineteen participants will have been born from in vitro fertilization and nineteen participants will have been naturally conceived.

PROCEDURES FOR THE STUDY:
If you agree to be in the study, you will do the following:

• First, you will be asked to fill out a demographic questionnaire regarding some current risk indicators, early life factors, and parental characteristics that will help to evaluate the results of the study. This questionnaire will be handed to you in a reserved conference room on campus where the research assistant will be stationed.
• You will then be asked to go to the student health clinic on campus to have your blood pressure taken and your blood drawn if you have been fasting for the past eight to twelve hours.
hours as indicated in the emails. If you have not been fasting, you will be asked to do so overnight and return the following morning to the student health clinic on campus to have your blood pressure taken and your blood drawn.
The total duration of participation in the study is about an hour.

RISKS AND INCONVENIENCES:
There are minimal risks and inconveniences to participating in this study. These include:
- Participants may be inconvenienced by the time spent participating in the study
- Participants may be uncomfortable answering some of the questions on the demographic questionnaire
- Participants with a needle (lancet) or blood phobia may be at risk of fainting when their finger is poked to get a small blood sample
- Participants may be concerned about finding a family history of hypertension or cardiovascular disease and may begin to identify themselves as having a problem either now or in the future
- Participants may be at risk of being told that they have a concerning BP, LDL, HDL, or triglyceride reading and may be told follow up with their primary care provider

SAFEGUARDS:
To minimize these risks and inconveniences, the following measures will be taken:
- Participants will be notified that researchers will be on campus from 7am to 9pm and that they can come at whatever time works best for their schedule
- If participants feel uncomfortable answering a question on the demographic questionnaire they will be reassured that all information is completely confidential
- Participants with a known needle (lancet) or blood phobia will be asked to look away while the lancet is used to place a small amount of blood on the cassette
- Participants that are concerned about the repercussions of finding out that they have a family history of hypertension or cardiovascular disease will be reassured that this is significant information they should be aware of as genetics play a vital role in many different medical conditions. This information will ultimately allow them to take the necessary precautions moving forward in their lives to prevent any unfortunate events from taking place.
- Participants that are apprehensive about finding out that they have a concerning blood pressure or blood level will be reassured that although these are the results of the study, they should follow up with their primary care provider for further testing. Additionally, they should look at this study as a "free" health assessment that may allow them to seek additional medical care sooner, ultimately treating a problem/condition in its early stages before it is too late.

The data will be locked away and stored in a lock box and placed on the top shelf of a locked cabinet (completely out of site to the public), inside each of the student health centers. The research assistant and myself will be the only two individuals to have access to the data. The access will be limited to us as we will be the only ones with a key.

CONFIDENTIALITY
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your
identity will be held in confidence in reports in which the study may be published. The data will be only reported in aggregate form and your information will not be identifiable.

**VOLUNTARY PARTICIPATION:**
Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty. Your decision whether or not to participate in this study will not affect your current or future relations with your university.

**BENEFITS OF TAKING PART IN THE STUDY:**
There are two direct benefits of participating in this study. First, individuals that participate in this study will benefit by gaining knowledge into their cardiovascular health. For instance, participants will be provided with their systolic blood pressure reading, diastolic blood pressure reading, high-density lipoprotein (HDL) level, low-density lipoprotein (LDL) level, and triglyceride level. This will give participants knowledge regarding the status of their current cardiovascular health. Individuals will be advised to follow up with their primary care providers if there are any concerning results that need further workup. Participants also will benefit by gaining knowledge into the family history and health of their parents and grandparents when filling out the demographic questionnaire.

**PAYMENT:**
You will receive a compensation for taking part in this study. There will be a $25 Visa gift card that will be offered to all participating subjects. The $25 gift card will be given to participating individuals after they have completed all the steps of the study including filling out the demographic questionnaire, having their blood pressure recorded, and having their blood drawn at their student health center on campus. The research assistant at each location will be responsible for handing out the gift cards after all three steps have been completed by the participating individual.

**PARTICIPANT’S CONSENT:**
If you have questions about the study, please call me at (949) 422-9519 or e-mail me at doers001@cougars.csusm.edu. You will be given a copy of this form for your records. If you have any questions about your rights as a participant in this research or if you feel you have been placed at risk, you can contact the IRB Office at irb@csusm.edu or (760) 750-4029.

Sincerely,

Shannon Michelle Doersam

**PARTICIPANT’S CONSENT**
By signing below, you are giving consent to participate in the study:

<table>
<thead>
<tr>
<th>Participant Signature</th>
<th>Printed Name</th>
<th>Date</th>
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Appendix F

IRB Application
1. Purpose of Project and Project Background

Describe your research question, including why the question is important, and how your study will attempt to answer it. Include how your literature review supports this with at least three citations. (Do not exceed one page--Use lay language.)

Now, more than ever, women are using assisted reproductive technology, specifically in vitro fertilization (IVF), to help them conceive (Sunderam et al., 2013). According to the Centers for Disease Control and Prevention survey in 2010, about 7.4 million of the 62 million women aged 15-44 years old (12%), had received infertility services at some point in their lives (2014). Nevertheless, IVF continues to be a controversial issue, as evidence remains inconclusive regarding the health outcomes for the offspring associated with this mode of conception. This study will examine the question: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process? This question is important as the problem remains that the current amount of data is insufficient to provide women and their families with adequate research information regarding IVF; consequently, women have difficulty making an educated decision concerning their chosen mode of conception. The study will attempt to answer this question by comparing the systolic blood pressures, diastolic blood pressures, high-density lipoprotein levels, low-density lipoprotein levels, and triglyceride levels among those conceived from IVF compared to those naturally conceived.

One study looked at the blood pressure and body fat measures of 238 8 to 18 year old IVF conceived participants in the Netherlands. Researchers investigated to see if there was an association between weight gain during infancy and early childhood in relation to body fat composition and blood pressure. The post-natal growth of children was explored at three months, six months, and one year. Among the IVF children, the standard deviation scores of height (P = 0.045), weight (P = 0.002), and BMI (P = 0.041) were significantly lower at three months and the standard deviation score of weight was significantly lower at six months (P = 0.027). Results indicated that there was a significantly higher gain in height, weight, and BMI during late infancy (3 months – 1 year) in children conceived from IVF compared with the control group (P = 0.013, P < 0.001, P = 0.029, respectively). Furthermore, rapid weight gain during early childhood appeared to be related to higher blood pressure readings at follow-up (independent of birth weight and gestational age) and that therefore was a better predictor of cardiovascular risk factors in IVF children only (Ceelen et al., 2009).

Dutch researchers produced yet another relevant study that was the first follow-up study to investigate cardiometabolic measures among 8 to 18 year old IVF singletons that compared these children to individuals that were spontaneously conceived (Ceelen, van Weissenbruch, Vermeiden, van Leeuwen, & Delemarre-van de Waal, 2008a). This study was paramount in determining that both systolic and diastolic blood pressures were found to be higher in children conceived from IVF compared to the control group. Additionally, the IVF children were found to be 2.1 times more likely to be in the highest systolic blood pressure quartile (OR = 2.1, 95% CI, 1.4 – 3.3) and 1.9 times more likely to be in the highest diastolic blood pressure quartile (OR = 1.9, 95% CI, 1.2 – 3.0) when compared to the control children. Furthermore, the children conceived from IVF had a greater sum of skinfolds (P = 0.04) and higher fasting glucose levels (P = 0.005) compared to the control group.

2. Recruitment Procedures & Participant Population

A) List the expected number of participants for each population group included in this study. 38 participants total (19 for the control group & 19 for the IVF group)

B) Describe all characteristics relevant to being selection of participants. (e.g., demographics, ethnicity, vulnerabilities, etc.) Explain why you are targeting this specific population.

The target population for this study includes college students attending universities in San Diego County who were conceived from IVF and were born between 1984 and 1993. This is the target population because there have been no studies beyond the age of 18 in the literature looking at the long-term effects of IVF related to cardiovascular disease. These college students ranging in age from 21 to 30 years old will be recruited into either the IVF group or the control group. For each participating IVF adult, there will be one control adult of the same gender, similar age (<3 months age difference), and similar physical activity level (i.e. light workout <2x/week, moderate workout 3-4x/week, or heavy workout>5x/week), who was naturally conceived. By pair matching the participants’ age, gender, and
physical activity level in both groups, this will help to control for threats to internal validity. Participants of the case group must be singletons conceived from IVF, born in the United States between 1984 and 1993, living in San Diego County, and speak English. Participants of the control group must follow all of the same inclusion criteria as the case group except for the fact that they were naturally conceived. Potential participants in both the IVF and NC groups will be excluded if they currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication.

C) Indicate whether anyone might be excluded from participating and explain why.

Potential participants in both the IVF and NC groups will be excluded if they currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication. Individuals that do not possess adequate English will be excluded as they will not be able to accurately answer the demographic questionnaire provided at the beginning of the study and they will not be able to follow the directions given by myself and the research assistant. Additionally, the participants will be excluded for the other reasons listed above as these all have the potential to alter the participant's blood work and blood pressure readings. Ultimately, these habits/conditions may provide inaccurate information, leading to unreliable results.

D) How will you find, recruit, or identify potential subjects? How will you select, from the volunteers, the final group of participants? Submit flyers, posters, or other oral or written invitations used to recruit potential participants.

The recruitment of subjects will occur on three large college campuses in San Diego to reach the most necessary amount of individuals between the ages of 21 and 30 years old (i.e. undergraduate and graduate students). The three campuses will include California State University San Marcos, San Diego State University, and the University of California San Diego. Approval from the Institutional Review Boards (IRB) will be obtained from all three colleges prior to any type of recruitment. School email addresses for potential candidates will be acquired from the registrar's office on each of the campuses. A registered email of invitation will be sent out to all students ranging in age from 21 to 30 years old about two months before arriving on campus to recruit. The email will give a detailed explanation of the purpose of the study, what the study entails, the risks and benefits associated with the study, information regarding the $25 Visa gift card that will be given as an incentive for participating in the study, and will conclude by asking for participation in the study. Due to the busy nature of undergraduate and graduate lifestyles, a follow-up email will be sent out one month before data collection begins and a final email will go out one week before arriving on campus to recruit. The recruitment process will take place in a previously reserved conference room at each university. The specific location will be included in the final email that goes out one week before arriving on campus so potential participants are aware of our location. Participants will be consented if they agree to participate in the study. For each participating IVF young adult, we will search for one control adult of the same gender, similar age (± 3 months age difference), and similar physical activity level (light, moderate heavy) that was naturally conceived. In the case that an approached adult does not want to participate, the control recruitment process will be repeated until an appropriate control adult is found that is willing to participate in the study. Furthermore, this process will continue until there are 38 confirmed participants; 19 in the IVF group and 19 in the naturally conceived group.

Once the participants agree to participate in the study, they will be given a demographic questionnaire to fill out regarding some current risk indicators, early life factors, and parental characteristics that will help to evaluate the results of the study. The questionnaires will be color coded to determine the mode of conception of each participating individual (i.e. white paper if naturally conceived, yellow paper if conceived by IVF). If the young adult is not able to complete the questionnaire, they will be asked to call their family to obtain this information. If this is still not feasible, they will be asked for their telephone numbers and will be notified that a representative of the study will follow-up with a phone call to obtain this information. They will then be asked to go to their student health clinic on campus to have their blood pressure taken and their blood drawn if they have been fasting for the past eight to twelve hours as indicated in the emails. If they have not been fasting, they will be asked to do so overnight and return the following morning to the student health clinic on campus to have their blood pressure taken and their blood drawn. The same nurse at all three campuses that will help in obtaining blood pressures and drawing blood will be
oriented to protocol and method for obtaining blood pressure prior to data collection. The nurse will not be informed
of the mode of conception of each individual in order to decrease any misclassification bias.

E) Will you be offering an incentive?

☐ Yes  ☐ No

If yes, please explain procedure for any incentives that will be offered. Include how much participants must do to be eligible to
receive credit.

There will be a $25 Visa gift card that will be offered to all participating subjects to reduce chances of attrition,
especially when some participating subjects are unable to answer all the questions from the demographic questionnaire
and must seek additional help from family members prior to completing the study. The $25 gift card will be given to
participating individuals after they have completed all the steps of the study including filling out the demographic
questionnaire, having their blood pressure recorded, and having their blood drawn at their student health center on
campus. The research assistant at each location will be responsible for handing out the gift cards after all three steps
have been completed by the participating individual.


Explain for each population participating in your research.
See the IRB web page on Informed Consent. See also Language Requirements.

A) How and when will you explain the study and the required elements of Informed Consent? Will you be doing this or will it
be handled by a research assistant?

I will explain the study and all the required elements of Informed Consent in all three emails that will be sent out to potential
candidates. School email addresses for potential candidates will be acquired from the registrar’s office on each of the
campuses. A registered email of invitation will be sent out to all students ranging in age from 21 to 30 years old about
two months before arriving on campus to recruit. The email will give a detailed explanation of the purpose of the
study, what the study entails, the risks and benefits associated with the study, information regarding the $25 Visa gift
(card that will be given as an incentive for participating in the study, and will conclude by asking for participation in the
study. Due to the busy nature of undergraduate and graduate lifestyles, a follow-up email will be sent out one
month before data collection begins and a final email will go out one week before arriving on campus to recruit.
Participants will be officially consented on campus during the first day of recruitment if they agree to participate in
the study. This will be handled by the research assistant.

B) How much time will participants have to consider participating between the explanation described above, the receipt of
the consent document, and the beginning of study?

The participants will have two months to consider participating in the study from the date of the first registered email of
invitation is sent out to the actual day of recruitment on campus. As previously indicated, the participants will be officially
consented on campus on the first day of the study. Once they have signed the consent, they will immediately be given a
demographic questionnaire to fill out.

C) If there are subjects under the age of 18, how will the study be explained to them? How will parental consent and child
assent be handled?

Not applicable.
D) If you are requesting a Waiver of Consent or a Waiver of Documentation of Consent, explain why this waiver is needed. Outline alternative procedures for obtaining consent or providing study information (e.g., information sheet, introduction screen for web survey, etc.).

Not applicable.

E) Indicate the primary language(s) of your participants. If any participants' is not fluent and comfortable with English, explain how you will ensure that participants' understanding of the activity for which they are giving consent.

The primary language of the participants is English. If they are not fluent and comfortable with the English language they will not be able to participate in the study.

4. Procedures and Methodology
   Provide descriptions of each distinct procedure and each population group.

A) Provide a step-by-step explanation of your research activities and methodologies that involve human subjects. Be thorough.

The recruitment of subjects will occur on three large college campuses in San Diego to reach the most necessary amount of individuals between the ages of 21 and 30 years old (i.e. undergraduate and graduate students). The three campuses will include California State University San Marcos, San Diego State University, and the University of California San Diego. Approval from the Institutional Review Boards (IRB) will be obtained from all three colleges prior to any type of recruitment. School email addresses for potential candidates will be acquired from the registrar's office on each of the campuses. A registered email of invitation will be sent out to all students ranging in age from 21 to 30 years old about two months before arriving on campus to recruit. The email will give a detailed explanation of the purpose of the study, what the study entails, the risks and benefits associated with the study, information regarding the $25 Visa gift card that will be given as an incentive for participating in the study, and will conclude by asking for participation in the study. Due to the busy nature of undergraduate and graduate lifestyles, a follow-up email will be sent out one month before data collection begins and a final email will go out one week before arriving on campus to recruit. Participants will be consented if they agree to participate in the study. For each participating IVF young adult, we will search for one control adult of the same gender, similar age (<3 months age difference), and similar physical activity level (light, moderate heavy) that was naturally conceived. In the case that an approached adult does not want to participate, the control recruitment process will be repeated until an appropriate control adult is found that is willing to participate in the study. Once the participants agree to participate in the study, they will be given a demographic questionnaire to fill out regarding some current risk indicators, early life factors, and parental characteristics that will help to evaluate the results of the study. The questionnaires will be color coded to determine the mode of conception of each participating individual (i.e. white paper if naturally conceived, yellow paper if conceived by IVF). If the young adult is not able to complete the questionnaire, they will be asked to call their family to obtain this information. If this is still not feasible, they will be asked for their telephone numbers and will be notified that a representative of the study will follow-up with a phone call to obtain this information. They will then be asked to go to their student health clinic on campus to have their blood pressure taken and their blood drawn if they have been fasting for the past eight to twelve hours as indicated in the emails. If they have not been fasting, they will be asked to do so overnight and return the following morning to the student health clinic on campus to have their blood pressure taken and their blood drawn. The same nurse will be at all three campuses as the recruitment will be on different days. The nurse will help in obtaining blood pressures and drawing blood will be
oriented to protocol and method for obtaining blood pressure prior to data collection. The nurse will not be informed of the mode of conception of each individual in order to decrease any misclassification bias.

When measuring the systolic and diastolic blood pressure, the auscultation method will be used, as this is the gold standard for measuring blood pressure by the Heart, Lung and Blood Institute of the NIH. With the World Health Organization committing to removing all mercury-containing devices from healthcare settings in 2005, an aneroid sphygmomanometer will be used instead, as this device has proven to be equally or more accurate than the mercury sphygmomanometers (Buchanan, 2009). The sphygmomanometer will be checked and calibrated by a qualified technician to ensure accurate readings prior to examination. With the proper technical maintenance, the sensitivity and specificity of this device is identical to the standard mercury manometer device (Tholl, Forstner, & Anlauf, 2004). Participants will be asked to sit quietly for at least five minutes in a chair, with both feet on the floor and the arm supported at the heart level (National Heart, Lung and Blood Institute, 2004). After confirming that the participant has not exercised, smoked, or had caffeine 30 minutes prior to the assessment, the blood pressure will be measured three times on the non-dominant arm, with three-minute intervals in between each assessment. The nurse will verify that they are using the appropriate size cuff for each participant, will position the cuff 2-3 cm above the antecubital fossa, and will position the central portion of the rubber bladder of the stethoscope on the brachial artery. The mean of the three readings will be used in analysis.

The participants will then have their blood drawn after the allotted fasting period. The same nurse, at each location, will draw blood samples for each participant. The labs to be drawn include HDL, LDL, and triglycerides of each participant. Once the blood is drawn, the nurse will then document the results of the LDL, HDL, and triglycerides for each participant. This information will be transferred to the Excel data collection worksheet to be imported into SPSS for analysis.

The Alere Cholesterol LDX® Analyzer System will be the machine used to gather the LDL, HDL, and triglyceride levels of each participant. This point-of-care (POC) testing provides such accurate data that Alere is the sole company that participates in all CDC standardization programs that follow the National Cholesterol Education Program performance goals, the Cholesterol Reference Method Laboratory Network (CRMLN), and Lipid Standardization Program certifications. For example, one study including 53 donors had finger stick specimens taken and were evaluated using four Alere Cholesterol LDX® analyzers. The same participants had venous specimens sent to commercial and CRMLN laboratories and results indicated that the LDL cholesterol assessment was in close agreement between the POC testing (93.3%) and the laboratory testing (93.6%) (Alere, 2014; Carey, Markham, Gaffney, Boran, & Maher, 2006). Additionally, another study confirmed that the Alere Cholesterol LDX® system was an adequate POC testing machine for the National Health Service Health Check (Jain et al., 2011).

B) Where will the research will be conducted? Describe any risks or confidentiality issues related to using this location.

The research will be conducted in two different places on campus: a reserved conference room and the student health center. The recruitment process will take place in a previously reserved conference room at each university. Although all measures within our control will be taken to uphold strict confidentiality, a possible risk may be that students will see other students that they know in the conference room. Nevertheless, we feel that a conference room is one of the most private and confidential areas on campus to conduct the study as opposed to recruiting participants in the center of the student quad. Furthermore, the second part of the study will take place in a small section of the student health center on campus. While the student health center may not be considered a confidential area to some, the results of the blood pressure readings, LDL, HDL, and triglyceride levels will be completely confidential as the nurse will be the only one able to see these results. Therefore, this location is considered very confidential when referring to the results of each participant.

C) State the specific dates/timeframe in which you plan to conduct your research.

California State University San Marcos - Research will be conducted on November 28, 2016, & February 14, 2017, from 7am to 9pm
San Diego State University - Research will be conducted on December 4, 2016, & February 16, 2017, from 7am to 9pm
University of California San Diego - Research will be conducted on December 5, 2016, & February 20, 2017, from 7am to 9pm
5. Participant Debriefing or Feedback.

If deception is involved in your research, participants should be debriefed about the nature of the study as soon as possible. Participants should be given the opportunity to request a copy of the results of the study/your final report.

A) Describe any feedback or information you will offer participants.

Participants will be notified immediately if there are any concerning results that would require them to follow up with primary care provider. All students who request a copy of the final study results will be provided one.

6. Risks

List risks for each population participating in the research and for each methodology. Please be sure the risks listed here match the risks mentioned in your consent letter or information sheets. Consider all risks very carefully. For more information on risks, see Examples of Risk.

A) Explain potential risks to your participants. Risks may be physical, psychological (e.g., strong emotional reactions to research questions), or inconveniences (e.g., time required).

1. Loss of time - may take 20 minutes to 1 hour
2. Strong emotional reactions to research questions (i.e., "Did your mother smoke during her pregnancy with you?", asking participant's weight)
3. Needle (lance) or blood phobia when poking the participant's finger to get small blood sample for testing
4. Risk of being told that they may have a concerning BP, LDL, HDL, or triglyceride reading and to follow up with their primary care provider
5. Participants may be concerned about finding a family history of hypertension or cardiovascular disease and may begin to identify themselves as having a problem either now or in the future

B) Vulnerable Subjects: Select which, if any, of the following vulnerable subjects will be involved in your research.

- Pregnant women, human fetuses, neonates (see Federal Guidelines, 45CFR246, subpart B)
- Prisoners (see Federal Guidelines, 45CFR246, subpart C)
- Children (see Federal Guidelines, 45CFR246, subpart D)
- Other Vulnerable Populations such as persons with cognitive disabilities, economically or educationally disadvantaged persons, etc.

C) Describe any special risks to vulnerable populations or your population profile

Not applicable.

D) List risks related to confidentiality of data. What could happen if an unauthorized person accessed the data? For instance, participant's identify or personal information could be known by others

Risks related to confidentiality of data include unauthorized person accessing the data and someone breaking into the lock box where the confidential information will be stored. If an unauthorized person accessed the data they would only be able to see personal information including the patient's name and phone number. However, the lock box will be kept on the top shelf in a very secure
E) Will any personal identifying data be recorded? If so, what information will be recorded? (e.g., Social security number, drivers license number, student id, address, phone number, birth date, personal email address)

The only personal identifying data will be the participants' names and phone numbers. After data collection, the personal information will be removed and replaced with a case identification number. Therefore, participants will be referred to by their case identification number rather than their personal name.

7. Safeguard Procedures to Minimize Risks.

A) Please respond to each risk that you listed in #6 above. State how you will minimize each risk and protect confidentiality.

1. Loss of time - will try to minimize risk by letting the participant know that we will be on campus from 7am to 9pm and they can come whenever works best for their schedule.
2. Strong emotional reactions to research questions (i.e. "Did your mother smoke during her pregnancy with you?") - will minimize risk by letting the participant know that this information is completely confidential.
3. Needle (lancet) or blood phobia when poking the participant's finger to get small blood sample for testing - will minimize this risk by asking that the participant to look away while the lancet is used to place a small amount of blood on the cassette.
4. Risk of being told that they may have a concerning BP, LDL, HDL or triglyceride reading and to follow up with their primary care provider - will try to minimize this risk by letting the participant know that although these may be the results we found in our study, they should still follow up with their primary care provider for further testing. Additionally, they should look at this study as a "free" health assessment that may allow them to seek additional medical care sooner, ultimately treating a problem/condition in its early stages.
5. If the participant finds out that they do have a family history of hypertension or cardiovascular disease, they may begin to identify themselves as having a problem either now or in the future - will try to minimize this risk by letting the participant know that this is vital information they should be aware of as genetics play a vital role in so many different medical conditions. Again, by learning this information sooner rather than later, they may be decreasing any potential harm in the future.

B) How you will safeguard data? Where/how will data be stored? Who will have access to the data? How will access be limited?

Data will be safeguarded by being locked away in a lock box and placed on the top shelf of a locked cabinet (completely out of site to the public), inside each of the student health centers. The research assistant and myself will be the only two individuals to have access to the data. The access will be limited to us as we will be the only ones with a key.

C) List referrals and/or resources that may be offered if a participant has a strong emotional response or a physical injury (e.g., clinics or shelters, medical or psychological referrals).

If a participant has a strong emotional response or physical injury during the course of the study, they will be given a list of on-campus trained medical professionals including psychologists, nurse practitioners, and doctors. These trained individuals will be able to assess and treat the needs of the individual and if necessary, refer out.
8. Study Benefits

A) Discuss any potential individual and/or societal benefits. Note, often there is no direct benefit for the participants. However, the study may contribute to the literature and/or future research.

Individuals that participate in this study will benefit by gaining knowledge into their cardiovascular health. For instance, participants will be provided with their systolic blood pressure reading, diastolic blood pressure reading, high-density lipoprotein (HDL) level, low-density lipoprotein (LDL) level, and triglyceride level. This will give participants knowledge regarding the status of their current cardiovascular health. Individuals will be advised to follow up with their primary care providers if there are any concerning results that need further workup. Participants also will benefit by gaining knowledge into the family history and health of their parents and grandparents when filling out the demographic questionnaire. Therefore, even if the participant does not have any concerning results during this particular study, they may be enlightened on the fact that they have a significant family history of cardiovascular disease and hypertension and ultimately monitor these more closely in the future. Furthermore, there are a plethora of societal benefits. With more individuals utilizing fertility services in the United States over the past decade, individuals will now be provided with sufficient data regarding IVF. As the use of IVF becomes more widespread, knowing and understanding the short and long-term health outcomes in children conceived with this technology is crucial, so that women and their families who require medical and technological interventions to conceive understand the inherit risks and benefits (Eisenberg, 2012). Additionally, older individuals that were conceived through IVF are beginning to express their desire to understand whether the way they were conceived has health implications affecting and possibly influencing their futures (Wilson et al., 2011).

B) Do the benefits from this study exceed the risks to participants? Please explain.

The benefits from this study far exceed the risks to the participants. The benefits have been discussed above. The risks affecting the participants may be more psychological than physical in nature. For example, a small drop of blood will be drawn from the patient’s finger using a lancet, for the point of care testing. One may argue risk for infection; however, the possibility of this event occurring is very low. Others may argue that participants filling out the demographic questionnaire may have feelings of resentment or anger when answering yes to the question, “Did your mother smoke during her pregnancy with you?” It is difficult to know how individuals will respond to this question; however, the benefits of the study still far outweigh any possible risk to the participants.

9. Researcher(s) qualifications and experience.

A) Briefly outline the primary researcher(s)'s qualifications and experiences relative to the subject of this research.

The primary researcher, Shannon Michelle Doersam, is a registered nurse of six years in San Diego County. She works at a local hospital on the open-heart surgery floor where she has gained a vast amount of knowledge in the field of cardiology. She assesses, treats, and educates individual patients on their cardiovascular health on a daily basis. Additionally, she is currently in the family nurse practitioner program at California State University San Marcos where she engages in assessing, diagnosing, and treating individuals of all ages. She has worked with neonates both inside and outside of the hospital as well as working with patients that are currently utilizing IVF treatments.

B) If this is a student project, include faculty sponsor's qualifications.

JoAnn Daugherty, Ph. D., RN, CNL. Dr. Daugherty is a faculty member at California State University San Marcos with over 20 years experience in cardiovascular nursing. She has worked with patients who have hypertension and hyperlipidemia including outpatient testing for these disorders.
Attached Email:

**Research Study: Assessing the Long Term Cardiovascular Effects of In Vitro Fertilization**

Hello Student of [insert university name here],

Come be a part of an important and exciting research study that will be taking place at [insert name of university here] on [insert date here]. If you are between the ages of 21 and 30 years old you may be eligible to participate. This purpose of this study is to answer the question: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process? The study will attempt to answer this question by comparing the systolic blood pressures, diastolic blood pressures, high-density lipoprotein levels, low-density lipoprotein levels, and triglyceride levels among those conceived from IVF compared to those naturally conceived. You may be eligible for this study if you were born in the United States between 1984 and 1993, live in San Diego County, and speak English.
Unfortunately, you will not be allowed to participate in this study if you currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication.

If you are eligible and decide to participate in this study you will be asked to arrive the morning of the study fasting. This means that you will not be allowed to have eaten or drank anything since midnight the night before the study. You will then be given information regarding the study including the risks and benefits of participating and will be asked to sign a consent form. Following this, you will be given a demographic questionnaire to fill out regarding some information about yourself and your family. Once the questionnaire is completely filled out, you will be asked to go to the student health center on campus where you will have your blood pressure taken and your blood drawn. You will receive a $25 Visa gift card for participating in the study.

Please understand that this email is not telling you that you have to join this study. It is your decision. Your participation is completely voluntary. Whether or not you participate in this study will have no effect on your relationship with the university. We look forward to speaking with those who may be interested in participating in this study. Please feel free to contact me with any questions you may have using the contact information provided below.

Sincerely,

Shannon M. Doersam
California State University San Marcos
Family Nurse Practitioner Student
Doers001@cougars.csusm.edu
(949) 422-9519

Research Study: Assessing the Long Term Cardiovascular Effects of In Vitro Fertilization

Hello Student of [insert university name here],

This is a reminder email that we will be at [insert name of university here] in the [exact conference room location] on [insert date here] conducting an important and exciting research study and we would love your participation! If you plan on participating please remember to show up fasting on the morning of the study. We have attached the previous email that was sent out if you need a reminder of what this study is all about. Please contact me if you have any questions. We look forward to your participation.

Sincerely,
Come be a part of an important and exciting research study that will be taking place at [insert name of university] on [insert date here]. If you are between the ages of 21 and 30 years old you may be eligible to participate. This purpose of this study is to answer the question: are young, college students (21-30 years old) born from in vitro fertilization more at risk of developing cardiovascular disease compared to individuals spontaneously conceived when controlling for current risk indicators, early life factors, and parental characteristics through case matching during the enrollment process? The study will attempt to answer this question by comparing the systolic blood pressures, diastolic blood pressures, high-density lipoprotein levels, low-density lipoprotein levels, and triglyceride levels among those conceived from IVF compared to those naturally conceived. You may be eligible for this study if you were born in the United States between 1984 and 1993, live in San Diego County, and speak English. Unfortunately, you will not be allowed to participate in this study if you currently smoke, possess inadequate English to complete the testing, were born with a congenital heart defect, have been diagnosed with a congenital/inherited condition that would affect blood pressure including but not limited to polycystic kidney disease, glomerular disease, aldosteronism, thyroid problems, or are currently taking blood pressure or cholesterol medication.

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