Tender Loving Care and the Woman with a History of Recurrent Pregnancy Loss

Emily L. Gruetzmacher
TENDER LOVING CARE AND THE WOMAN WITH A HISTORY OF
RECURRENT PREGNANCY LOSS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the Degree of
Master of Medical Science

June 11, 2014

Emily L. Gruetzmacher, PA-SII
Class of 2014
Yale Physician Associate Program

Pinar Kodaman, MD, PhD
Assistant Professor
Obstetrics, Gynecology, and Reproductive Sciences
Yale School of Medicine
TABLE OF CONTENTS

ABSTRACT...........................................................................................................iv

CHAPTER 1: INTRODUCTION.................................................................................1
  1.1 Background..................................................................................................1
    1.1A Spontaneous Abortion............................................................................1
    1.1B Recurrent Pregnancy Loss.....................................................................1
    1.1C Psychological Implications of RPL.......................................................3
    1.1D RPL and Tender Loving Care.................................................................3
  1.2 Statement of the Problem..........................................................................4
  1.3 Goals and Objectives...............................................................................5
  1.4 Hypothesis................................................................................................6
  1.5 Operational Definitions...........................................................................6
REFERENCES.......................................................................................................7

CHAPTER 2: LITERATURE REVIEW......................................................................12
  2.1 Introduction..............................................................................................12
  2.2 Review of Relevant Studies......................................................................12
    2.2A TLC and RPL: Empirical Evidence......................................................13
    2.2B Psychological Implications of Pregnancy Loss..................................19
  2.3 Review of Possible Confounding Variables...........................................23
    2.3A Maternal Age.....................................................................................23
    2.3B Maternal Obstetrical History..............................................................25
    2.3C Lifestyle Factors.................................................................................25
    2.3D Various Causes of RPL and Potential Treatments.............................27
  2.4 Review of Relevant Methodology............................................................31
    2.4A Study Design......................................................................................31
    2.4B Patient Selection..................................................................................32
    2.4C Intervention........................................................................................33
    2.4D Comparison.........................................................................................35
    2.4E Monitoring of Adverse Events..........................................................35
    2.4F Primary Outcome Measures.............................................................36
    2.4G Secondary Outcome Measures........................................................37
    2.4H Other Variables..................................................................................38
    2.4I Sample Size and Statistical Significance..........................................39
    2.4J Statistical Analysis Considerations....................................................40
  2.5 Conclusion................................................................................................40
REFERENCES.......................................................................................................40

CHAPTER 3: STUDY METHODS............................................................................47
  3.1 Study Design............................................................................................47
  3.2 Study Setting............................................................................................47
  3.3 Study Population and Sampling...............................................................47
  3.4 Subject Protection and Confidentiality....................................................48
ABSTRACT

Recurrent pregnancy loss affects one to five percent of couples. This complication is traumatic for women and has psychological implications, including anxiety and depression. Increased monitoring and support – tender loving care – from clinicians has been shown to positively impact pregnancy outcomes during subsequent pregnancies in women with recurrent pregnancy loss. The affect of tender loving care on pregnancy outcomes and psychological distress is not entirely clear, however. We propose a randomized controlled trial to determine if these associations are statistically significant. Specifically, we will recruit women with any cause for early recurrent pregnancy loss and compare early pregnancy outcomes and levels of psychological distress between women who receive tender loving care during the first trimester and those who receive standard prenatal care. Data from this study will provide insight into the impact of tender loving care on pregnancy outcomes and psychological distress in this population and guide patient management.
CHAPTER 1: INTRODUCTION

1.1 Background

1.1A Spontaneous Abortion

Spontaneous abortion (SAB) is the most common adverse event affecting pregnant women.\(^1\) SAB, also referred to as miscarriage or pregnancy loss, is the expulsion of a fetus before the pregnancy reaches 20 weeks of gestation, or prior to a fetal weight of more than 500 grams.\(^2,3\) The majority of pregnancy losses are early, taking place before 12 weeks of gestation, rather than late, taking place after 12 weeks.\(^2,4-6\)

Many studies have aimed to accurately estimate the rate of SAB in the general population, and it has been determined and widely recognized that about 15% of all clinically recognized pregnancies (identified by ultrasonography or histopathologic evaluation\(^7\)) result in SAB.\(^1,4,8-11\) The true incidence of SAB is difficult to determine, however, because only 30-50% of conceptions result in clinically recognized pregnancies.\(^11,12\) Many women miscarry before they know that they are pregnant or before the establishment of a clinical pregnancy by ultrasound. Most first trimester SABs are the result of genetic abnormalities, which increase with advancing maternal age.\(^13-15\)

1.1B Recurrent Pregnancy Loss

Recurrent pregnancy loss (also referred to as recurrent miscarriage or recurrent SAB) as defined by the American Society for Reproductive Medicine and the American College of Obstetrics and Gynecology, is the failure of two or more clinically recognized pregnancies.\(^7,16\) This definition is not fully agreed upon, however; some argue that because two consecutive losses may occur by chance alone, three or more losses are necessary for the diagnosis of recurrent pregnancy loss (RPL).\(^3,8,17-19\) Evidence shows that
in women who have had two consecutive pregnancy losses, the prevalence of abnormal results for diagnostic testing does not differ when compared with women who have had three or more consecutive losses.\textsuperscript{20} Hence, it is recommended that couples be evaluated for RPL following two losses.\textsuperscript{16,20}

A large-scale population-based epidemiologic study estimating the incidence of RPL in clinically recognized pregnancies has not been conducted. Current knowledge regarding the epidemiology of this diagnosis is based on widely recognized estimates.\textsuperscript{18} It is estimated that one to five percent of women experience RPL, with variation due to differing definitions of RPL and the ages of women included in the estimates.\textsuperscript{1,9,21-23}

Maternal age and obstetrical history are important risk factors affecting a woman’s ability to carry a pregnancy. While most random SABs occur due to chromosomal abnormalities,\textsuperscript{14} chromosomal abnormalities are more commonly the cause for pregnancy loss in random SABs than they are in RPL when the maternal age is less than 36.\textsuperscript{24-26} SAB risk increases with maternal age, however, regardless of obstetrical history, and a woman’s risk of pregnancy loss reaches 75\% at the age of 45.\textsuperscript{27-29} This is likely due to oocyte chromosomal abnormalities.\textsuperscript{30} Previous obstetrical history is another risk factor for RPL. A woman’s risk of pregnancy loss may increase directly with each prior loss.\textsuperscript{5,28,29,31,32}

Women with a history of RPL are commonly seen in specialty clinics and undergo extensive evaluations in attempts to uncover the cause for their losses.\textsuperscript{6,16} The etiology of RPL may be attributed to uterine anatomic abnormalities,\textsuperscript{33-38} immunological factors,\textsuperscript{39,40} endocrine disorders,\textsuperscript{41-45} genetic abnormalities\textsuperscript{14,15,26,46,47} and infection.\textsuperscript{48} The most common diagnosis given to women with RPL, however, is unexplained or
idiopathic RPL. More than 50% of women with RPL remain without a definitive explanation for their losses.6,15,27-29,49

RPL is difficult to manage and treat because many of the etiologies are controversial and the efficacy of various treatment options is not entirely known. Treatment efficacy is difficult to ascertain because it cannot be known if a woman with a history of RPL is successful in carrying a subsequent pregnancy due to chance alone or treatment. Studies have shown that even women with unexplained RPL have up to a 60% chance of a future successful pregnancy depending on maternal age and parity status.27,28

1.1C Psychological Implications of RPL

There are significant psychological implications for women with RPL. Miscarriage is a traumatic event for women and can induce anxiety, anger, dysphoria, and grief, emotions that can endure for several months.50 Pregnant women who have had prior miscarriages have been found to have higher levels of anxiety in subsequent pregnancies than pregnant women who have never had a miscarriage.51-53 Multiple studies have documented significant levels of anxiety and depression in women with RPL (higher than levels found in the general population), many of whom experience psychological symptoms that would likely warrant a psychiatric diagnosis if they were to be evaluated by a psychiatrist.54-58 Women with RPL may feel shame and guilt as a result of their difficulty in carrying a pregnancy, and they may doubt their reproductive ability, fearing that they will never have biological children, or never have another child.

1.1D RPL and Tender Loving Care

It is not entirely clear whether anxiety and distress are purely the result of RPL or if they are also mediators in the pathophysiology of RPL.57,59-61 Regardless, it is widely
recommended that women with a history of RPL receive increased emotional support and monitoring – termed supportive care or tender loving care (TLC) in the literature – during subsequent pregnancies.\textsuperscript{1,3,8,9,62-64} Women with RPL also report that they desire this advanced care.\textsuperscript{62,63} The recommendation for TLC is based upon the results of several studies suggesting that supportive care and close monitoring of a pregnancy from a dedicated team of healthcare providers may significantly increase the ability of a woman with a history of RPL to have a successful pregnancy.\textsuperscript{65-67} In one such study, successful pregnancy outcomes were documented in 86% of women who received TLC, as compared with 33% of women who did not receive the intervention.\textsuperscript{67}

1.2 Statement of the Problem

Although the results of previous studies examining the impact of TLC on pregnancy outcomes in women with a history of RPL are compelling, questions remain regarding the efficacy of TLC in RPL patients. To date, a randomized controlled trial (RCT) has not been conducted in this area. As a result, the information that we have regarding the impact of TLC on women with RPL is subject to bias and confounding, and concrete data are lacking.\textsuperscript{61,68} Without random allocation of the intervention to study participants, it is difficult to calculate the impact that TLC has on pregnancy outcome.

In addition, previous studies looking at TLC and pregnancy outcomes in women with RPL exclude women who have been diagnosed with a known cause for RPL. Therefore, the data from these studies are not generalizable to all women with RPL – those with known etiologies for RPL and those with idiopathic RPL.

Although studies examining the impact of TLC on pregnancy outcomes in women with RPL use the terms TLC and supportive care, the terms are poorly defined and differ
between studies. Recommendations are made to treat RPL patients with TLC, but this is difficult when the term is variable and not clearly defined for patients and clinicians. TLC generally comprises some combination of continuity of care with the same medical staff, weekly ultrasounds to ensure fetal viability and offer reassurance, emotional support, partner involvement in care, formal psychotherapy and counseling, relaxation techniques, and recommendations regarding sexual intercourse, diet, and lifestyle during pregnancy. In order to best care for and manage RPL patients, it is necessary to clearly define TLC in the context of RPL by examining the literature to determine evidence-based practice and the preferences of women with the diagnosis of RPL.

Finally, although one study examined the impact that TLC may have on anxiety levels in women with RPL during a subsequent pregnancy, the study was a small prospective cohort study, and it only included women with idiopathic RPL. RPL is anxiety-inducing and frustrating for all women, and the difference in anxiety levels between women with idiopathic RPL and women with a known cause for RPL is not statistically significant. Therefore, it is valuable to study the impact that TLC may have on levels of psychological distress in women with explained and unexplained RPL.

1.3 Goals and Objectives

The overall goal of this RCT is to assess the impact of TLC on pregnancy outcome at 12 weeks of gestation in women with a history of early RPL. Specifically, this study aims to determine if TLC does in fact improve early pregnancy outcomes in RPL patients by reducing the rate of SAB in subsequent pregnancies as described in previous literature. Additionally, this study aims to determine if TLC has an impact on the level of psychological distress in this population.
This study will provide a better understanding regarding the specific impact of TLC on pregnancy outcomes in women with a history of RPL. Additionally, further insight will be gained into the role that TLC plays in mediating psychological distress in women with a history of RPL.

1.4 Hypothesis

There is a 15% difference in early pregnancy outcome at 12 weeks of gestation among pregnant women with a history of early recurrent pregnancy loss who receive tender loving care during the first trimester of pregnancy when compared with women who receive standard prenatal care during the first trimester of pregnancy.

1.5 Operational Definitions

Pregnancy outcome: presence or absence of an ongoing, viable pregnancy at 12 weeks of gestation, as determined by ultrasound.

Recurrent pregnancy loss (RPL): two or more consecutive pregnancy losses.\(^7\)

Tender loving care (TLC): serial serum human chorionic gonadotropin (hCG) monitoring until the pregnancy can be visualized by ultrasound; weekly transvaginal ultrasound monitoring of pregnancy beginning at five weeks of gestation; well-defined and planned care for the first trimester; continuity of care from the same staff members at each visit; empathy and support from the staff and recognition of the woman’s emotional needs; partner engagement during visits; reassurance and feedback on the status of the pregnancy; time to ask questions, address concerns, and elicit advice appropriate to the gestation age of the pregnancy; availability of a social worker for counseling purposes; opportunity for medical visits and ultrasounds in the case of miscarriage symptoms.
REFERENCES


CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Introduction

An extensive review of the literature took place between September 2013 and May 2014. The review took place to study the epidemiology and various etiologies of RPL. The etiologies of RPL and possible treatments were reviewed in order to comprehensively understand the population of women to be included in the proposed study, as well as to study the methodology employed when involving pregnant women with RPL in clinical studies. The literature review was also conducted to identify the psychological implications of RPL. Finally, the review took place to research the impact of TLC on pregnancy outcomes in women with RPL. The literature review revealed no RCT to date assessing the impact of TLC on pregnancy outcomes in women with RPL.

The Ovid MEDLINE database, Scopus, and the Cochrane Library were utilized for the search. Search topics included the following terms independently and in various combinations: pregnancy loss, spontaneous abortion, habitual abortion, recurrent pregnancy loss, recurrent miscarriage, recurrent spontaneous abortion, anxiety, psychological impact, psychological adaptation, psychological stress, psychological support, supportive care, tender loving care, prenatal care, pregnancy monitoring, social support, pregnancy outcome, and treatment outcome. The search was limited to studies in English and those involving human subjects. Prospective trials, retrospective trials, RCTs, cross-sectional analyses, meta-analyses, and high-quality reviews were evaluated.

2.2 Review of Relevant Studies

This section of the literature review will focus on previous studies that examine the relationship between TLC and pregnancy outcomes in women with RPL. The results
of these studies will form the rationale for the proposed study. This section will also review the literature discussing the psychological implications of pregnancy loss. These studies will provide the rationale for assessing psychological distress in the participants in the proposed study in order to determine if TLC has an impact on levels of psychological distress during the first trimester of subsequent pregnancies in women with RPL.

2.2A TLC and RPL: Empirical Evidence

The literature review returned four studies examining TLC and its impact on subsequent pregnancies in women with RPL. Each of these four TLC studies examines the relationship between TLC and pregnancy outcomes in women with idiopathic or unexplained RPL. No studies examining the relationship between TLC and pregnancy outcomes in women with both known causes for RPL and idiopathic RPL were found. No large-scale RCT with sufficient power, examining the relationship between TLC and pregnancy outcomes in women with RPL, was found.

Stray-Pedersen et al. conducted a quasi-experimental prospective study examining the etiology of pregnancy loss and reproductive outcomes in couples with RPL. The study included 195 couples with a history of three or more consecutive pregnancy losses that were referred to the Department of Obstetrics and Gynecology (OB-GYN) at the National Hospital in Norway between 1971-1980. Couples underwent diagnostic testing, and abnormalities were identified as a probable cause for RPL in 56% of the couples. The couples were offered treatment and 80% of those who conceived carried their subsequent pregnancies to term.1

Of most pertinence to the proposed study is the group of 85 couples who were not diagnosed with a cause for RPL. Women in this group were told to notify the hospital
immediately upon becoming pregnant. Sixty-one (72%) of the couples became pregnant during the study. Those identified as living within a reasonable distance from the hospital (n=37) were selected for TLC, which included psychological support, weekly medical visits and exams, encouragement to rest, avoidance of heavy work and travel, abstinence from sexual intercourse, and bed rest for the two week gestational period during which they had experienced their previous losses. They were provided no surgical or medical treatment. The remainder of the women (n=24) did not receive specific antenatal care and were advised to attend their local antenatal clinic. The primary outcome variable was the success of a pregnancy (delivery of a healthy baby at term). Eighty-six percent of the women receiving TLC had successful pregnancies and 14% experienced pregnancy loss. In comparison, 33% of the women who did not receive TLC had successful pregnancies and 67% experienced pregnancy loss. Statistical analysis was performed using chi-square testing with Yate’s correctional factor. The 53% difference in successful pregnancy outcome between the groups was statistically significant (p<0.001).¹

Although the results of the study conducted by Stray-Pederson et al. are statistically significant, a discussion of the study is warranted. The study only included couples with idiopathic RPL. Therefore, it is difficult to ascertain the impact that TLC might exert on couples with a known cause for RPL. Even in couples with a known etiology for RPL, it cannot be decided with certainty that the identified abnormality is the cause of RPL. In addition, the design introduces significant selection bias into the results, as couples were assigned to the intervention and control groups based on their distance from the hospital. Finally, TLC treatment was not optimally defined. It is unclear what is meant by and included in “optimal psychological support” and “weekly medical exams.”¹
Liddell et al. also examined pregnancy outcomes following TLC in a group of women with unexplained RPL (three or more unexplained losses). The prospective cohort study included 52 women, 42 of whom were selected to receive supportive care (TLC) at an early pregnancy clinic during the first trimester of subsequent pregnancies, and 10 of whom were assigned to attend a standard prenatal clinic. Supportive care consisted of the diagnosis of pregnancy at four to five weeks of gestation, weekly visits at an early pregnancy clinic (with hCG, progesterone, and ultrasound monitoring, during which the women were advised to view their embryo on the screen), continuity of care with the same medical staff, stress reduction and relaxation techniques (a weekly class teaching relaxation and daily use of a relaxation tape), consistent feedback on the progression and status of the pregnancy, and a specialized room at the hospital that the women could visit during the anniversary of previous losses or if their current pregnancy was in danger. They received no pharmacologic or surgical treatment. At the end of the first trimester, women in the intervention group were discharged to receive ongoing prenatal care from their own OB-GYN clinician. Women assigned to the control group did not receive specialized care and were advised to attend the clinic of their OB-GYN provider.2

In the group of women assigned to receive supportive care, 44 pregnancies were followed (two women attended the clinic for two pregnancies). Eighty-six percent of the pregnancies were successful (resulting in a live birth) and 14% resulted in miscarriage. In comparison, nine of the ten women in the control group became pregnant and 33% had a live birth. The 53% difference in successful pregnancy outcome between the groups was found to be statistically significant (p=0.005; statistical analysis by Fishers Exact Test).2
These results suggest a high rate of success in subsequent pregnancies in women with idiopathic RPL when they are offered supportive care alone during the first trimester of pregnancy. The study did not include women with an identified cause for RPL. Although the study included a randomization process and the groups were not found to vary at baseline in terms of average age, average number of recurrent losses, and primary vs. secondary RPL (primary RPL referring to those who have never had a live birth and secondary RPL referring to those who have had a live birth prior to recurrent losses), the randomization process is not described and it is not known how treatment groups were allocated. Finally, the women in this study knew which group they were assigned to before becoming pregnant. There was no concealment of group allocation prior to the subsequent pregnancy. As a result of unclear randomization techniques and a lack of allocation concealment, the results of this study may be affected by selection bias.2

Clifford et al. conducted a prospective cohort study examining the impact of supportive care on unexplained first trimester RPL and had similar findings. Women attending St. Mary’s Hospital’s recurrent miscarriage clinic in London underwent testing to identify the cause for RPL. Those diagnosed with unexplained first trimester recurrent miscarriage (three or more consecutive first trimester miscarriages) formed the study group (n=201). They were encouraged to attend an early pregnancy clinic during the first trimester of subsequent pregnancies, which included weekly ultrasounds to assess fetal viability and measure growth, and continuity of care with the same clinicians. They did not receive medical or surgical treatment prior to or during the pregnancy. The women who did not attend the clinic received no specialized care and were contacted by phone or mail to obtain information regarding the outcome of their pregnancy.3
Of the women who attended the early pregnancy clinic (n=160), 74% had a successful pregnancy outcome (live birth) and 26% miscarried. Those who did not attend the clinic (n=41) had a successful pregnancy outcome of 49% and 51% miscarried. The difference in miscarriage rates between these two groups was statistically significant (25% difference; p=0.002). The group of 201 women experienced 63 total miscarriages, all of which occurred during the first trimester. This suggests that women with a history of early RPL will continue to miscarry during the first trimester in subsequent pregnancies. Women under 40 who had less than six prior miscarriages and who attended the early pregnancy clinic had the best prognosis, with a miscarriage rate of 21%.

Although the women were not randomized to the groups, there was no statistically significant difference in the baseline characteristics (ethnicity, median age, and number of previous losses) of women who attended the pregnancy clinic and those who did not (p=0.5 for median age, p=0.7 for number of previous miscarriages). Lack of randomization, as in the other studies, may have introduced selection bias into the results, as women self-selected for treatment. The study group in this study was larger than in the other studies, but the intervention and control groups were unbalanced, with 160 women in the intervention group and only 41 women in the control group.

Al-Otaibi et al. conducted a prospective cohort study that examined the impact of supportive care on anxiety levels and early pregnancy outcomes in women with RPL. Seventeen pregnant women (gestational age of nine weeks or less) with a history of unexplained first trimester RPL (three or more consecutive losses) were selected for study participation. Baseline characteristics were collected and included maternal and paternal age, level of education, occupation, number of previous pregnancies, number of
previous losses, number of living children, and gestational age. Anxiety levels were measured prior to and after the administration of supportive care using the Hamilton Anxiety Rating Scale.\textsuperscript{4} Each week, the women received ultrasounds to assess the fetal heart rate and measure fetal growth. Supportive care was comprised of sessions offering advice regarding diet and lifestyle, emotional needs, relaxation techniques, exercise, medication use, and warning signs of pregnancy loss. Early pregnancy outcome was defined as the presence of an ongoing pregnancy at 12 weeks of gestation on ultrasound.\textsuperscript{5}

Eighty-eight percent of women had a successful early pregnancy outcome and 12% miscarried. Study results revealed a reduction in anxiety symptoms after supportive care. Prior to supportive care, 35.3\% of participants had severe anxiety, 52.9\% moderate anxiety, and 11.8\% mild anxiety. After supportive care, 93.3\% had mild anxiety and 6.7\% had moderate anxiety. The results were statistically significant (p=0.001).\textsuperscript{5}

This study is significant because it not only examines the link between TLC and pregnancy outcomes, but it also examines the impact that supportive care may have on anxiety in women with RPL. While the participants experienced a high rate of successful pregnancy outcome at 12 weeks of gestation and statistically significant reductions in anxiety, the study was a small observational study without a control group. This makes it difficult to determine if the outcomes are due to the impact of the intervention or if they are due to chance or bias. In addition, patients were eligible to enter the study at any time prior to nine weeks of gestation. These women did not receive assessment of anxiety or supportive care at the same time points during their pregnancies.\textsuperscript{5}

The empirical studies examining the impact of TLC on pregnancy outcomes reveal the need for a RCT. Without a RCT, it is difficult to know the true effect of TLC
on pregnancy outcomes. A RCT will limit the impact of bias and confounding on study results. The study also needs to be adequately powered with a large sample size. The literature review reveals that TLC, or supportive care, varies between the studies, making it difficult to determine which components of TLC are most important or effective.

2.2B Psychological Implications of Pregnancy Loss

This portion of the review will focus on studies examining the psychological implications of SAB and RPL. This will provide the rationale for assessing psychological distress in women at the start and end of the proposed study to determine if TLC affects levels of psychological distress during subsequent pregnancies in women with RPL.

Tsartsara et al. examined the impact of miscarriage history on pregnancy-specific anxiety (Pregnancy Outcome Questionnaire$^6$) and maternal fetal attachment (Maternal Antenatal Attachment Scale$^7$) in pregnant women during their first and third trimesters. The study recruited thirty-five pregnant women, 71.4% with no history of miscarriage and 28.6% with a history of miscarriage. Marital status, age, pregnancy planning, gestational age, number of prior pregnancies, and parity were controlled for. In the first trimester of pregnancy, ANOVA revealed a statistically significant difference in pregnancy-specific anxiety levels between the groups (p=0.001). Pregnancy-specific anxiety was higher in women with a history of miscarriage, irrespective of parity status. However, differences in maternal fetal attachment scores were not found to be statistically significant (p=0.208, p=0.119, and p=0.952 for subscales). In the third trimester, anxiety levels were not significantly different between the groups (p=0.411). In addition, maternal fetal attachment was higher for both groups in the third trimester, with statistically significant differences from the first to the third trimester (p=0.01, p=0.004,
and p=0.000 for subscales). The data from this study suggest that women with a history of miscarriage experience higher levels of pregnancy-specific anxiety early in a subsequent pregnancy when compared with women with no history of miscarriage, regardless of whether or not the woman has a living child. The study also suggests that anxiety is highest in these women during the first trimester and decreases by the third.8

It is important to note that the two groups in the study were unequal in size, 10 having a history of loss and 25 having no history of miscarriage. Selection bias may have affected study results, as only 24 of the original participants followed up during the third trimester, with 50% of the miscarriage group being lost to follow-up. It is not known if they dropped out of the study due to increased anxiety or a subsequent pregnancy loss.8

A comparative descriptive cross-sectional study by Cote-Arsenault et al. sought to compare state anxiety, pregnancy specific anxiety, and optimism in multigravid women with and without a history of perinatal loss. The study recruited 160 multigravid pregnant women at 17-28 weeks of gestation, 96 with no history of perinatal loss, and 74 with a history of perinatal loss (early SAB to neonatal death). A self-administered questionnaire was utilized to collect demographic data, OB history, and utilization of healthcare during pregnancy. The women also completed the Spielberger State-Anxiety Inventory9 (used to assess state anxiety - subjective feelings of temporary anxiety), the Pregnancy Anxiety Scale (developed to assess pregnancy-specific anxiety), and the Life Orientation Test10 (utilized to assess optimism). T-tests or chi square analyses were used to compare the groups, which were similar at baseline in regards to demographic variables and optimism (t=0.93, p>0.05). The difference in state anxiety between the two groups was not statistically significant (p=0.067). However, the difference in pregnancy-specific anxiety
between the groups was statistically significant (p=0.003). In addition, women with higher levels of state and pregnancy anxiety reported greater utilization of healthcare, desiring more frequent phone calls and visits with their healthcare providers.\textsuperscript{11}

Of note, the women in this study were homogeneous, with the majority being highly educated, of middle to high socioeconomic status, married, employed, and Caucasian, creating a lack of external validity. Women in the loss group had diverse OB histories, with varying times during which they experienced losses (from two weeks of gestation to neonatal death, M=10.38 weeks, SD=6.93). Some of the women had losses prior to a live birth and some had losses after a live birth. Time since perinatal losses ranged from one to twelve years. With such variability in the loss group and the presence of covariates, it is difficult to ascertain the impact of perinatal loss on anxiety levels.\textsuperscript{11}

Hutti et al. conducted a longitudinal cohort study examining the impact of depression, anxiety, and perinatal loss on a woman’s utilization of healthcare during pregnancy. The study included 36 women with a history of perinatal loss, 32 women with no history of perinatal loss, and 38 women experiencing their first pregnancy. Data were collected from these women from the third trimester of pregnancy until eight months postpartum. Anxiety was measured using the Spielberger State-Trait Anxiety Inventory.\textsuperscript{9} Women with previous perinatal losses had higher baseline levels of anxiety when compared with women in the other groups (p=0.008).\textsuperscript{12} This is interesting because Tsartsara et al. did not find anxiety to persist late in pregnancy in women with a history of perinatal loss.\textsuperscript{8} Tsartsara et al., however, assessed pregnancy-specific anxiety, whereas Hutti et al. assessed state and trait anxiety.\textsuperscript{8,12} Women were also asked to report their utilization of healthcare during the current pregnancy. During the third trimester, women
with a history of perinatal loss reported more phone calls to healthcare providers, unscheduled office visits, and diagnostic procedures than women in the other groups (p=0.013, p≤0.001, and p=0.005). 12

Similar to those in the study by Cote-Arsenault et al., the participants in this study were homogenous, limiting the external validity of the study. 11 In addition, recall bias may have impacted the study results, as women were asked to self-report their utilization of healthcare. Women may have under- or over-reported their utilization of healthcare. 12

Blackmore et al. conducted a large cohort study assessing symptoms of anxiety (measured by the Crown-Crisp Experimental Index13) and depression (measured by the Edinburgh Postnatal Depression Scale14) in subsequent pregnancies in women with a history of perinatal loss. About 13,000 women with and without histories of perinatal loss were recruited and assessed numerous times during pregnancy and postnatally. The number of previous losses significantly predicted symptoms of depression (p<0.01) and anxiety (p<0.01), with psychosocial and OB factors controlled for. The association was found to persist throughout pregnancy and postnatally. 15 These results support the findings of Hutti et al., suggesting that significant psychological symptoms may persist in women with a history of perinatal loss, even after the birth of a healthy child. 12,15

In a cross-sectional study, Craig et al. examined the impact of RPL on 86 women attending a recurrent miscarriage clinic. Participants completed Beck’s Depression Inventory,16 the Spielberger Trait Anxiety Inventory,9 the General Health Questionnaire,17 and St. Mary’s Miscarriage Questionnaire (developed to assess pregnancy-specific psychiatric morbidity). Psychiatric morbidity did not differ significantly in women with a history of two pregnancy losses when compared to women
with a history of three or more losses (post hoc independent t-tests; p>0.1), suggesting that women with a history of two losses experience significant psychological symptoms. Thirty-three percent of women had depressive symptoms and 21% had significant levels of anxiety, regardless of parity, number of prior miscarriages, and time since last miscarriage. Regardless of obstetrical history, women may have significant psychological consequences of RPL up to 10 months after the last loss. This study did not utilize a control group, making it difficult to ascertain the significance of the study results.¹⁸

The above studies suggest that women with pregnancy loss experience significant psychiatric morbidity, which may persist late into a subsequent pregnancy and even into the postpartum period.¹²,¹⁵ Psychiatric morbidity is found in women with pregnancy loss regardless of parity and other obstetric factors.⁸,¹⁸ In addition, those with increased anxiety during pregnancy report greater utilization of healthcare.¹¹,¹²

2.3 Review of Possible Confounding Variables

A number of variables may impact a woman’s ability to successfully carry a pregnancy. Potential confounders to the association between TLC and early pregnancy outcomes in women with a history of early RPL will be discussed here.

2.3A Maternal Age

Maternal age significantly affects a woman’s ability to conceive and carry a pregnancy. The study by Clifford et al. found that women 30 and under had a miscarriage rate of 25% in subsequent pregnancies, but women 40 and over had a miscarriage rate of 52% (p=0.02).³ A descriptive cohort study by Lund et al. examined prognostic factors for live birth in women with RPL. Only 42% of women 40 and older gave birth to a child within five years, compared to 81% of women aged 20-24 (p<0.01). Using women aged
30-34 as a reference group (HR=1), the HR of giving birth to a child during a five year period was 1.43 (95% CI, 1.03-1.98) for women aged 20-24 and 0.55 (95% CI, 0.36-0.83) for women 40 and older. A population-based case-controlled study revealed a three-fold increased risk of miscarriage in subsequent pregnancies in women with a history of at least one miscarriage in women under 24 years of age (OR 2.9; 95% CI, 1.4-5.8) and women over 35 years of age (OR 2.8; 95% CI, 1.1-6.8), when compared with women aged 24-34 (p<0.0001). Another population-based case-controlled study found that relative to women aged 25-29, women between the ages of 35 and 39 had a 75% increased risk of first trimester miscarriage (OR 1.75; 95% CI, 1.37-2.22) and women 40 and over had a five-fold increased risk of miscarriage (OR 5.1; 95% CI, 3.54-7.52). No differences in miscarriage odds were found in those aged 18 to 35 (p=0.73).

It is likely that increased pregnancy loss in women 35 to 40 and older is due to greater numbers of oocyte chromosomal abnormalities in this age group. A study that retrospectively analyzed tissue samples from SABs found that 82% of samples from women aged 35 and over had abnormal karyotypes compared with 57% of samples from women under 35 (p<0.0005). Multivariate logistic regression analysis revealed maternal age to be predictive of first trimester loss due to aneuploidy (OR for each increasing year of maternal age 0.90 ± 0.003; p<0.001). Similarly, a retrospective cohort study examining the etiology of RPL in women over 35 found aneuploidy to be the cause of pregnancy loss in 70% of losses experienced by women without a history of RPL and in 78% of losses in those with a history of RPL (three or more first trimester losses), revealing that women of advanced maternal age may experience high rates of pregnancy loss due to chromosomal abnormalities, regardless of obstetrical history.
2.3B Maternal Obstetrical History

Maternal obstetrical history is another factor influencing miscarriage risk. Studies have found that prior miscarriage negatively predicts subsequent pregnancy outcomes. One study found a four-fold increased risk of miscarriage in women with one or more previous miscarriages when compared to women with only successful pregnancy outcomes (OR 4.8; 95% CI, 2.5-9.4; p<0.0001). Lund et al. found that an increased number of prior miscarriages resulted in a statistically significant difference in chance of live birth among women in their study (p<0.01). Seventy-two percent of women with a history of three miscarriages gave birth to a child within a five year period, compared with 50% of women with six or more prior miscarriages (HR 0.55; 95% CI, 0.41-0.74). A population-based case-controlled study found that miscarriage odds increased with each prior miscarriage. Using women with no prior miscarriage as a reference (OR 1.00), women with one prior miscarriage were found to have an OR of 1.65 for repeat miscarriage (95% CI, 1.47-2.31), 2.00 for two prior miscarriages (95% CI, 1.31-3.06), and 3.87 for three or more prior miscarriages (95% CI, 2.29-6.54). The study also found that a history of ever having had a live birth reduced the odds of miscarriage (OR 0.63; 95% CI, 0.48-0.84). Miscarriage odds were not found to decrease with an increasing number of live births (p=0.71). Other studies have found, however, that a history of live birth may not have an impact on future pregnancy outcomes. Clifford et al. and Brigham et al. found similar pregnancy outcomes in those with primary and secondary RPL.

2.3C Lifestyle Factors

Lifestyle factors such as tobacco use, alcohol use, caffeine intake, and maternal weight have been studied as factors influencing pregnancy outcomes. George et al. found
a two-fold increased risk of first trimester loss among smokers when compared with non-smokers (adjusted OR 2.1; 95% CI, 1.1-4.1; \( p=0.02 \)).\(^{20}\) Another study found a dose-dependent relationship between tobacco and miscarriage, with miscarriage risk increasing with the number of cigarettes smoked per day.\(^{25}\) Conversely, some studies have found that smoking, even up to 20 cigarettes per day, does not increase the risk of SAB.\(^{21,26}\)

Rasch et al. found an increased risk of SAB among women who drank five or more units of alcohol per week (OR 4.84; 95% CI, 2.87-8.16), but not in women who drank up to four units per week (OR 1.00; 95% CI, 0.74-1.34).\(^{26}\) Kesmodel et al. had similar findings, with an increased risk of first trimester SAB among women who consumed five or more drinks per week. Using less than one drink per week as a reference (HR 1.00), women drinking one to two drinks per week were found to have a HR of 1.3 (95% CI, 0.8-2.0), three to four drinks per week HR of 0.8 (95% CI, 0.4-1.7), and five or more drinks per week HR of 3.7 (95% CI, 2.0-6.8).\(^{27}\)

Studies suggest that the impact of caffeine on risk of SAB is dose-related. Rasch et al. found that women who consumed 375 mg or more of caffeine per day were at a significantly increased risk of SAB (OR 4.84; 95% CI, 2.87-8.16) when compared with women who consumed 0-199 mg per day.\(^{26}\) In a prospective cohort study, Weng et al. found that increased daily doses of caffeine were associated with an increased risk of SAB. Compared with women who did not consume caffeine during pregnancy (HR 1.00), women who consumed less than 200 mg per day had a HR of 1.42 (95% CI, 0.93-2.15) for SAB and women who consumed more than 200 mg per day had a HR of 2.23 (95% CI, 1.34-3.69). This trend was found to be statistically significant (\( p<0.01 \)).\(^{28}\)
The World Health Organization (WHO) designates Body Mass Index (BMI) categories as follows: underweight: <18.50 kg/m\(^2\), normal: 18.50-24.99 kg/m\(^2\), overweight: ≥25.00 kg/m\(^2\), and obese: ≥30 kg/m\(^2\).  

A retrospective analysis investigating the impact of BMI on risk of miscarriage in subsequent pregnancies in women with RPL found that when compared to women with a normal BMI, underweight and obese women had higher odds of miscarriage (OR 3.98; 95% CI, 1.06-14.92 and OR 1.71; 95% CI, 1.05-2.8). Overweight women were not found to have increased odds of miscarriage (OR 1.02; 95% CI, 0.72-1.45). Helgstrand et al. found an increased risk of SAB in underweight women compared to women with a normal BMI (HR 1.24; 95% CI, 0.95-1.63). Lashen et al. found obese women to be at a higher risk for both first trimester miscarriage (OR 1.2; 95% CI, 1.01-1.46) and RPL (OR 3.5; 95% CI, 1.03-12.01).

2.3D Various Causes of RPL and Potential Treatments

A complete review of the various causes of RPL and their treatments is beyond the scope of this review. Some of the common causes will be discussed, however, as women with any cause for early RPL will be eligible for the study, and participants with known etiologies for RPL may present having received medical or surgical treatment. This discussion will introduce potential confounders and influence the sample size calculation.

It is estimated that 50% to 80% of early SABs are the result of chromosomal abnormalities, with variation due to maternal and gestational age at the time of loss. In women under 36, however, chromosomal abnormalities are more commonly the cause for pregnancy loss in sporadic SABs than they are in cases of RPL. A retrospective study examining the products of conception from 420 pregnancies found greater numbers of
cytogenically abnormal specimens from women with sporadic losses when compared with specimens from women with a history of RPL. In women 18 to 29, 65% of specimens were chromosomally normal in women with RPL, compared with 52% in women with sporadic losses (p=0.03). Findings were similar for women 30 to 35, with 63% of specimens being chromosomally normal in women with RPL, versus 48% in the control group (p=0.001). This difference was not found in women over 36. Another retrospective study analyzing the products of conception from 1,309 women with early RPL found that women with a greater number of prior SABs were more likely to have a chromosomally normal abortus than women with fewer prior losses (p=0.0063). Women with chromosomally normal products of conception were more likely to experience another SAB than women with a chromosomally abnormal abortus.

Couples with RPL may undergo karyotyping to determine if either partner carries a chromosomal abnormality. Through analysis of 20,432 parental karyotypes from patients with RPL, Barber et al. found that two percent of the patients had chromosomal abnormalities, the most common being a balanced reciprocal translocation. A case-controlled study comparing reproductive outcomes in couples with RPL found that couples with abnormal karyotypes had a greater chance of subsequent miscarriage when compared with couples with normal karyotypes. Forty-nine percent of couples with structural chromosomal abnormalities had subsequent miscarriages versus 30% of couples without abnormalities (95% CI, 11%-26%; p<0.01). A prospective cohort study of 51 couples with RPL and the presence of a structural chromosomal abnormality found a live birth rate of 71% in these couples with close evaluation and monitoring. Only 36%
of the miscarriages in the cohort had unbalanced structural chromosomal rearrangements. A high live birth rate was found without the utilization of reproductive technology.\textsuperscript{37}

A systematic review found that congenital uterine anomalies are present in about 6.7\% (95\% CI, 6.7-7.9) of the general population and 16.7\% (95\% CI, 14.8-18.6) of women with a history of RPL.\textsuperscript{38} Congenital uterine anomalies may predispose women to RPL by decreasing intraluminal volume and disrupting uterine blood supply. There are many types of congenital uterine anomalies, of which the septate uterus is the most common. Women with a septate uterus have a miscarriage rate of about 65\%.\textsuperscript{39} These patients may undergo resection, reducing the risk of subsequent SAB. A systematic review found that in women who underwent septoplasty for a septate uterus, about 80\% achieved term deliveries and only 15\% experienced SAB.\textsuperscript{40} Roy et al. examined reproductive outcomes in women with a septate uterus and a history of RPL, infertility, or preterm delivery following hysteroscopic septum resection. A reduction in miscarriage rate from 91.5\% prior to resection to 12.9\% following resection (p=0.02) was observed.\textsuperscript{41}

Uterine fibroids are another anatomic abnormality that may contribute to pregnancy loss. A systematic review examining pregnancy outcomes in women with fibroids who had undergone in-vitro fertilization found that women with fibroids had a SAB rate of 20.4\% versus 12.9\% in women without fibroids (OR 1.6; 95\% CI, 1.3-2.0).\textsuperscript{42} The association between fibroids and RPL is not entirely understood, but it is thought that large, submucosal fibroids may be associated with an increased risk of pregnancy loss. Treatment with myomectomy may improve pregnancy outcome in these patients.\textsuperscript{43,44}

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by the presence of antiphospholipid antibodies. Clinical manifestations, such as fetal loss,
are the result of vascular thrombosis and pro-inflammatory factors. APS is diagnosed as the cause of RPL in 15% of women, and these patients have a recurrent loss rate of about 90% when not treated. A systematic review examining treatment efficacy in prevention of subsequent SAB in women with a history of pregnancy loss and APS found that treatment with heparin and aspirin may reduce pregnancy loss by 54%. Two trials found that combination therapy with aspirin and heparin significantly reduced the risk of SAB when compared to treatment with aspirin alone (RR 0.46; 95% CI, 0.29-0.71).

Eight to twelve percent of pregnancy losses are the result of endocrine factors, such as thyroid dysfunction, polycystic ovarian syndrome, uncontrolled diabetes, and luteal phase deficiency. A systematic review found subclinical hypothyroidism to be associated with an increased risk of perinatal demise (OR 2.7; 95% CI, 1.6-4.7) when compared to euthyroid controls. A retrospective study found that with adequate treatment, 100% of patients with overt hypothyroidism achieved term deliveries. In contrast, a 60% SAB rate was found in inadequately treated women. The role of endocrine factors in RPL is not entirely understood, but women with well-controlled endocrine disorders generally have good pregnancy outcomes.

In about 50% of couples with RPL, no definitive cause is identified and patients are diagnosed with idiopathic RPL. Patients with idiopathic RPL have high rates of success in subsequent pregnancies when treated with TLC alone. Women with idiopathic RPL may be offered pharmacological treatment, such as progesterone, aspirin, or heparin to improve pregnancy outcomes. A systematic review found a statistically significant reduction in SAB with the use of progesterone in women with idiopathic RPL compared to controls (OR 0.38; 95% CI, 0.20-0.70). Another systematic review,
examining the efficacy of anticoagulation in women with RPL to improve pregnancy outcomes, found insufficient data to recommend this treatment for women with idiopathic RPL\textsuperscript{56}. A live birth rate of 81\% was found in women receiving aspirin and a placebo control (RR 1.00; 95\% CI, 0.78-1.29).\textsuperscript{56,57} Similar live birth rates were also observed in women receiving heparin (82\%) and aspirin (84\%) (RR 0.97; 95\% CI, 0.81-1.16).\textsuperscript{56,58}

Due to inconclusive evidence regarding the efficacy of pharmacologic treatment in women with idiopathic RPL and the necessity of further trials, women with idiopathic RPL who are receiving empiric treatment will not be eligible for the proposed study.

Women with known causes for RPL and idiopathic RPL will be eligible for the proposed study. As substantiated by the data above, even treatment for a known cause of RPL does not result in a 100\% success rate in subsequent pregnancies. Women will be identified at baseline as having a known cause for RPL or idiopathic RPL.

2.4 Review of Relevant Methodology

This portion of the literature review will discuss relevant study design elements and methods to be utilized in the proposed study. The methodology of the proposed study will be fully discussed in Chapter 3.

2.4A Study Design

As described in Chapter 2.2A, the relationship between TLC and pregnancy outcomes in women with RPL has only been studied in the context of a quasi-experimental prospective study and multiple prospective cohort studies.\textsuperscript{1-3,5} The proposed study will be a multicenter RCT examining the relationship between TLC and early pregnancy outcomes in women with a history of early RPL. This design will ensure that the groups are equivalent at baseline and will limit the potential for confounding and bias.
Several RCTs have been conducted in RPL patients to assess the efficacy of various treatments in preventing subsequent SAB and improving pregnancy outcomes.\textsuperscript{59-63}

In order to limit selection bias, allocation to groups will be concealed in the proposed study. As in other multicenter RCTs utilizing women with RPL, randomization will be performed centrally by a computer program and communicated via phone.\textsuperscript{61-63} An independent coordinator will manage randomization, and the investigators at each site will be blinded to the randomization process.\textsuperscript{58} Patients will be stratified by known versus unknown etiology for RPL, enabling subgroup analysis of pregnancy outcomes between the two groups. In a RCT conducted by Laskin et al., RPL patients were stratified according to the presence or absence of antiphospholipid antibodies for this purpose.\textsuperscript{62}

2.4B Patient Selection

In many studies involving women with RPL, including each of the TLC studies described in Chapter 2.2A, women are recruited for study participation from RPL clinics or specialized reproductive departments in hospitals.\textsuperscript{1-3,5,53,58,64,65} The proposed study will take place at reproductive and infertility specialty centers, and eligible women attending these centers will be notified of the study and recruited for participation.

Women with a history of early RPL – two or more consecutive clinical pregnancy losses during the first trimester – will be eligible for the proposed study.\textsuperscript{24,53,60-63,65-68} Although some studies define RPL as three or more losses, two or more losses will be used in the proposed study because the prevalence and frequency of RPL etiology does not significantly differ in women with two versus three losses.\textsuperscript{53,62} In women with a prior live birth, the two most recent pregnancies must have ended in pregnancy loss in order to be eligible for participation.\textsuperscript{60} The four prior TLC studies only included women with
idiopathic RPL.\textsuperscript{1-3,5} The proposed study, however, will include women with known and unknown etiologies for RPL. As discussed in Chapter 2.3A, maternal age is a potential confounder to the association between TLC and early pregnancy outcome. Women between the ages of 18 and 39 will be eligible for the proposed study.\textsuperscript{3,19-22}

Exclusion criteria will include history of psychiatric illness, presence of uncontrolled chronic disease or endocrine disorder, and history of thrombophilia or venous thromboembolism.\textsuperscript{56,59,69} To limit confounding, women will be asked to abstain from tobacco and alcohol and consume no more than 200 mg of caffeine per day.\textsuperscript{20,26-28} Women with BMIs \textless{} 18.50 kg/m\textsuperscript{2} and \textgreater{}= 30 kg/m\textsuperscript{2} will not be eligible for the study.\textsuperscript{30-32}

Women eligible for the study will be enrolled and consented prior to becoming pregnant, but will not be randomized until a pregnancy is established.\textsuperscript{62} It is expected that about 85\% of the women enrolled for the proposed study will become pregnant during the study period.\textsuperscript{1,2,24,53} Therefore, the number of women enrolled for the study will be 15\% greater than the calculated number of women needed for randomization.\textsuperscript{61}

2.4C Intervention

The components of TLC included in each of the prior TLC studies are fully described in Chapter 2.2A. TLC differed in each of the studies, but there are important similarities.\textsuperscript{1-3,5} In each of the studies, TLC included some form of a weekly medical visit and physical exam. Specifically, in the studies by Liddell et al., Clifford et al., and Al-Otaibi et al., TLC included weekly first trimester ultrasounds beginning at four to five weeks.\textsuperscript{2,3,5} Weekly ultrasounds have also been included as a component of patient management in other studies including women with RPL.\textsuperscript{24,53} A qualitative study by Musters et al. examined the preferences of patients with RPL and found that women
strongly desire weekly or bi-weekly ultrasounds once the pregnancy can be seen on ultrasound. Women in the TLC group in the proposed study will receive weekly transvaginal ultrasounds from five to twelve weeks of gestation. They will be encouraged to visualize their developing pregnancy on the screen. Women also prefer frequent serum hCG monitoring until the pregnancy can be visualized on ultrasound. The appropriately rising hCG provides women with reassurance. Serum hCG will be measured every two days until a value of 2,000 mIU/mL is reached or surpassed in women receiving TLC in the proposed study.

Women with RPL prefer that their care during the first trimester be well defined and planned from the beginning of the pregnancy. Continuity of care from the same medical staff at each visit is a key component of TLC. Women with RPL prefer continuity of care because they want their providers to know them well. Women desire their physicians to exhibit empathy and support, listen to their concerns, and address their emotional needs. In addition, women prefer that their partners attend prenatal visits with them and be directly involved in the care of the pregnancy.

The psychological and emotional needs of RPL patients are addressed in a variety of ways in the previous TLC studies. In the studies by Liddell et al. and Al-Otaibi et al., TLC included frequent reassurance and feedback on the status of the pregnancy, as well as time during each visit to address questions and concerns and elicit advice appropriate to the gestational age of the pregnancy. Women prefer this as an element of their TLC care, as well as the availability of a social worker for counseling purposes. Finally, RPL patients desire to be seen by their providers and receive ultrasounds in the case of
symptoms of miscarriage. All of the above components will be included in the TLC provided to patients in the intervention group in the proposed study.

The studies by Stray-Pederson et al., Clifford et al., and Musters et al. included formal stress reduction and relaxation techniques as a component of TLC. This will not be included in the proposed study, as women will have the availability of a social worker. TLC in the study by Stray-Pederson et al. included bed rest during the gestational period at which prior losses had occurred. However, Musters et al. found that women do not prefer this treatment. Stray-Pederson et al. also advised women in their TLC group to avoid heavy work, traveling, and sexual intercourse. However, the evidence regarding the avoidance of intercourse and bed rest during pregnancy to prevent SAB is lacking.

Women in the proposed study will not be advised to abstain from sex or to take bed rest.

2.4D Comparison

In the TLC studies by Stray-Pederson et al. and Liddell et al., the women who did not receive TLC were told to attend their local antenatal clinic or their standard OB-GYN for prenatal care. In the proposed study, women randomized to the control group upon becoming pregnant will be released to the care of their standard OB-GYN to receive routine prenatal care, which is typically initiated between eight to ten weeks of gestation.

2.4E Monitoring of Adverse Events

Bleeding is a common event in the first trimester. A study assessing pregnancy outcomes in patients with first trimester bleeding found that those with light and heavy bleeding were more likely to have a SAB before 24 weeks than those without bleeding (OR 2.5; 95% CI, 1.5-4.3 and OR 4.2; 95% CI, 1.6-10.9 respectively). Not all bleeding during pregnancy is the result of impending miscarriage, however. First trimester
bleeding may be the result of cervical lesions, ectopic pregnancy, SAB, or vaginitis.\textsuperscript{75} In the TLC study by Liddel et al., 40\% of the patients who had successful pregnancies experienced bleeding in the first trimester.\textsuperscript{2} In the proposed study, women will be told to notify their healthcare provider in the case of bleeding.

In the case of ectopic pregnancies, diagnosed by the absence of an appropriately rising serum hCG prior to the establishment of clinical pregnancy by ultrasound or the absence of an intrauterine pregnancy on ultrasound, TLC patients will be managed by their TLC clinicians and those in the control group will be managed by their standard OB-GYN provider.\textsuperscript{2,3,76} Subsequent SABs will be managed in this way as well.\textsuperscript{1-3,5,61,63,76} Studies involving pregnant women with a history of RPL often mention termination of pregnancy due to fetal anomalies.\textsuperscript{3,24,58,76} In the proposed study, couples who choose to terminate a pregnancy will be referred to clinicians who can manage the termination.

\textbf{2.4F Primary Outcome Measures}

The TLC study by Al-Otaibi et al. assessed pregnancy outcome at 12 weeks of gestation as the primary outcome measure in their participants.\textsuperscript{5} The primary outcome measure in the proposed study will be the presence of an ongoing viable pregnancy (viewed on transvaginal ultrasound) at twelve weeks of gestation.\textsuperscript{24} Many studies involving RPL patients utilize live birth as the primary outcome (or assess the primary outcome at the completion of pregnancy).\textsuperscript{1-3,5,60-62} Pregnancy outcome at 12 weeks is a reasonable outcome, however, as most pregnancy losses in prior studies occurred during the first trimester.\textsuperscript{2,3,24,53} Women in the proposed study will have a history of early RPL and it is likely that they will continue to have first trimesters losses if they have a subsequent SAB. In addition, many studies utilizing TLC or increased supportive care for
women with RPL discontinue this care at the end of the first trimester of pregnancy, suggesting that this is the most critical period in the pregnancy for risk of SAB.\textsuperscript{2,3,24,53,60,62}

2.4G Secondary Outcome Measures

Secondary outcome measures will include the occurrence of adverse events (see Chapter 2.4E). Psychological distress will also be measured as a secondary outcome in order to assess the impact that TLC may exert on levels of psychological distress in women with RPL. Many screening tools are available for measuring psychological symptoms in patients, some of which are mentioned in Chapter 2.2B.

The Edinburgh Depression Scale will be utilized in the proposed study for the assessment of psychological distress.\textsuperscript{14,77,78} The Edinburgh Postnatal Depression Scale (EPDS) was originally developed as a self-report screening scale for postnatal depression. The 10-item scale takes five minutes to complete and is acceptable to patients and easy to score. The 10 items are scored on a four-point scale (a score of zero to three for each item and a total score of zero to thirty), with higher scores indicating greater levels of depressive symptoms. Women are asked to complete the EPDS based on their feelings in the past week. Using 12 as a threshold for identifying depression, the EPDS was found to have a sensitivity of 86\%, a specificity of 78\%, and a positive predictive value of 73\%.\textsuperscript{14}

Although originally validated in postpartum women, the EPDS has since been validated in pregnant women. Using 12 as a threshold for identifying women with depression, the scale was found to have a sensitivity of 64\%, a specificity of 90\%, and a positive predictive value of 50\%.\textsuperscript{14} When the EPDS is not utilized in the postpartum period, the scale is called the Edinburgh Depression Scale (EDS).\textsuperscript{77}
Although other scales, such as the General Health Questionnaire, the State-Trait Anxiety Inventory, and the Hospital Anxiety and Depression Scale, have been validated for use in pregnant women, the EDS was created specifically for pregnant women and is well-tolerated. In addition, the EDS does not only screen for depression, as studies have shown that the EPDS/EDS contains an anxiety subscale and women with various psychiatric disorders are captured at a threshold score of 12. Therefore, it is appropriate to use the EDS as a measure of psychological distress in pregnant women with RPL. The EDS also has good test-retest reliability and validity.

It is recommended that women who score 12 and higher on the EPDS/EDS be referred for psychiatric evaluation. Therefore, women scoring 12 or higher on the EDS in the proposed study will be advised to notify their general practitioner or OB-GYN clinician of their score on the EDS at the end of the study.

2.4H Other Variables

Information to be collected at baseline will include age at randomization, ethnicity, marital status, BMI (underweight or overweight), known vs. unknown etiology for RPL, primary vs. secondary RPL, and number of previous losses. The rationale for collecting these variables is outlined in Chapter 2.3. Age will be assessed as an ordinal variable. Categories will be 18-24, 25-29, 30-34, and 35-39 years old. Primary vs. secondary RPL will be collected as a nominal variable. Women with no prior history of a live birth will be identified as primary RPL patients and women with a history of prior live birth before the occurrence of two or more consecutive early losses will be identified as secondary RPL patients. The number of previous losses will be collected as an ordinal variable with the categories being two, three, four, five, and six or more losses.
2.4I Sample Size and Statistical Significance

Due to the small number of studies similar to the proposed study, the elements utilized to calculate an appropriate sample size to sufficiently power the study and find a statistically significant result will be based upon estimates from previous studies including women with RPL. A study by Habayeb et al. examining the efficacy of a RPL clinic and its impact on pregnancy outcomes found live birth rates of 75% in those with idiopathic RPL, 64% in those with thrombophilies, 83% in those with autoimmune antibodies, 71% in those with polycystic ovarian syndrome, and 57% in those with abnormal karyotypes. The average live birth rate for women with these diagnoses was 70%. The results of this study are helpful in estimating the expected pregnancy outcome in the comparison group in the proposed study because the study included women with known causes for RPL and idiopathic RPL, and the women may have received diagnosis-specific treatment. Although they did receive frequent ultrasounds, the women did not receive specialized and well-defined supportive care. A successful pregnancy outcome of 70% will be expected in the comparison group in the proposed study. Rates of successful pregnancy outcomes were much lower in the TLC studies described in Chapter 2.2A because they included only women with idiopathic, untreated RPL. A successful pregnancy outcome of 85% will be expected in the TLC group in the proposed study. This is based on the average successful pregnancy outcome found in the TLC groups in prior TLC studies. Although these studies only included women with untreated, idiopathic RPL, these are the best numbers available to estimate the expected successful pregnancy outcome for the proposed study. A 15% difference in successful pregnancy outcome will be expected and considered statistically significant in the proposed study.
The proposed study will utilize a power of 80% and a significance level of 5% in order to sufficiently power the study and calculate an appropriate sample size. The study will account for an expected 10% dropout rate by increasing the sample size by 10%.62

2.4J Statistical Analysis Considerations

The proposed study will examine early pregnancy outcome in women with RPL who become pregnant during the study period. Analysis will include only those women who become pregnant during the study and are randomized for treatment, not all women who are enrolled and consent for study participation.60,63

An intention-to-treat analysis will be utilized in the proposed study, including patients lost to follow-up, ectopic and molar pregnancies, terminations, and losses prior to the establishment of clinical pregnancy (biochemical losses).58,62 In a RCT by Stephenson et al., pregnancy outcomes were analyzed only among those who achieved clinical pregnancy, excluding biochemical losses.63 In the proposed study, a sub-group analysis will look at the pregnancy outcomes at 12 weeks of gestation in women who achieve a clinical pregnancy, as recognized by ultrasound at five weeks of gestation.

2.5 Conclusion

While studies have shown that providing women with a history of RPL with TLC during subsequent pregnancies may improve pregnancy outcome, a sufficiently powered and well-designed RCT with an appropriate sample size is necessary to determine the impact of TLC on pregnancy outcome. A RCT is also necessary to determine the impact that TLC may have on levels of psychological distress in women with RPL. The information above provides the rationale for the study design and methods that will be further outlined in Chapter 3.
REFERENCES


CHAPTER 3: STUDY METHODS

3.1 Study Design

The proposed study will be a multicenter randomized controlled trial to assess the difference in rates of successful pregnancy outcome at 12 weeks of gestation in women with a history of early RPL who receive TLC during the first trimester of pregnancy when compared with women who receive standard prenatal care during the first trimester.

3.2 Study Setting

The proposed study will take place at five reproductive endocrinology and infertility specialty centers in CT, MA, and NY. The selected institutions are within the Society for Assisted Reproductive Technologies (SART) network. See Appendix A for institution list.

3.3 Study Population and Sample Size

The source population for the proposed study is women with a history of early RPL, defined as two or more consecutive clinical pregnancy losses during the first trimester. The study population will be selected via convenience sampling of women receiving care at selected institutions within the SART network (Appendix A).

Women aged 18 to 39 with a history of two or more consecutive first trimester clinical pregnancy losses (pregnancy confirmed by ultrasound or histopathologic evaluation) will be eligible for enrollment in the proposed study. In women with a history of prior live birth, the two most recent pregnancies must have ended in pregnancy loss.

Women with both explained and unexplained RPL will be eligible for the participation (women must present already having undergone a workup for RPL). Women with a known cause for RPL may receive specific treatment prior to their enrollment in the
study. Women with an unknown etiology for RPL will not be eligible for the proposed study if they receive additional treatment prior to or during their enrollment in the study.

Exclusion criteria for the proposed study will include the following: history of psychiatric illness, uncontrolled chronic disease (neurologic, cardiac, pulmonary, renal and gastroenterology conditions), uncontrolled endocrine disorders (diabetes and hyper/hyperthyroidism), history of thrombophilia or venous thromboembolism, BMI <18.50 kg/m$^2$ or $\geq$30 kg/m$^2$, conception by in-vitro fertilization or artificial insemination, and participation in another clinical study during the study period. In order to participate in the study, women must agree to abstain from tobacco and alcohol and consume no more than 200 mg of caffeine per day during the period of time during which they are enrolled.

Women will be consented for participation in the proposed study once they have been screened for eligibility and meet the above criteria. Women will be eligible for randomization to treatment groups upon the establishment of pregnancy. Patients will only be eligible for study participation during one pregnancy.

### 3.4 Subject Protection and Confidentiality

The Human Investigation Committee (HIC) at Yale University and an equivalent committee at the other sites must approve the study protocol prior to the initiation of the study. Applications for research using human subjects must be completed, submitted, and approved at each institution. All eligible patients must give written informed consent prior to their study participation. The informed consent form will be formatted to meet the requirements of each institution (see Appendix B for the form to be used at Yale).

The study protocol will be in compliance with current Health Insurance Portability and Accountability Act (HIPAA) regulations and all personnel involved in the
study will complete HIPAA training prior to the study’s initiation. Patient confidentiality will be protected by the assignment of a unique identification number to each participant. Forms utilized to collect patient information will be labeled with the patient IDs and these numbers will be used for data entry and analysis. Patient records will be stored in locked cabinets at each institution when not in use and electronic patient information will be stored on encrypted and password-protected computers.

3.5 Recruitment

Prior to the start of the study, a letter describing the study and outlining the eligibility requirements will be distributed to the staff at each participating institution (Appendix C). Informational meetings will also be held at each institution. Medical staff will be asked to refer women that meet the inclusion and exclusion criteria for the study. Rolling basis recruitment will take place between January 1, 2015 and August 1, 2016.

The institution principle investigator (PI) will approach women who meet the eligibility criteria to discuss the purpose and methods of the study. Potential risks and benefits will be disclosed. Women uncertain about or not interested in study participation will be given a flyer to take home and asked to contact the institution PI if they have questions (Appendix D). Women interested in participation will be required to give written informed consent (Appendix B). The institution PI will read the form to the patient and answer any questions. The patient will then read the form herself. The patient and institution PI will both sign and date the consent form.

Following consent, a clinician will collect baseline characteristics (see Appendix E for form) and perform a physical exam. If the patient remains eligible for study participation, she will be asked to contact the institution upon becoming pregnant.
We expect that not all women enrolled for the study will become pregnant during the study period and a pregnancy rate of 85% is estimated. The proposed study will aim to enroll at least 308 women, anticipating that 85% (267) will become pregnant and randomized for treatment. The sample size calculation will be discussed in Chapter 3.13.

Between 2005 and 2010, about 450 women with RPL presented to Yale Fertility Center – an average of about 90 women each year. Recruitment for the proposed study will take place at five institutions over 19 months. Using the data from Yale as a guide, it is reasonable to estimate that more than 308 women with RPL will present to the selected institutions and be eligible for study enrollment during the recruitment period.

### 3.6 Assignment of Treatment Groups

Upon becoming pregnant, women will present to their respective institution for confirmation of pregnancy by serum hCG and then randomized to study groups. Randomization will be performed centrally by a computer program and communicated via phone. Institution PIs will contact an independent randomization coordinator and supply patients’ IDs. Patients will be stratified by known versus unknown etiology for RPL and randomly assigned to receive TLC or standard prenatal care. Group assignments will be communicated to the institution PIs, who will contact participants. The randomization coordinator will not be involved in the enrollment or intervention phases and the institution PIs will be blinded to the randomization process. A database of patient IDs and group assignments will be stored on an encrypted computer at the central facility.

### 3.7 Intervention

Women randomized to the intervention group will receive TLC during the first trimester of pregnancy (until 12 weeks of gestation). At the first TLC visit, the
components of TLC will be reviewed with each patient. The timeline of visits to the
clinic will be outlined and the women will be informed of what to expect during their
clinic visits. Women will receive a form at this visit, outlining her visits to the clinic
during the first trimester of pregnancy. A medical assistant (MA) and the scheduling staff
at each office will complete this form. See Appendix F for a copy of the form.

After a positive pregnancy test, women will present to the clinic every two days
for serial hCG measurements to ensure that the hCG is rising appropriately. After
reaching a hCG threshold of at least 2,000 mIU/ml, patients will receive weekly
transvaginal ultrasounds from approximately five weeks of gestation until twelve weeks
of gestation. Women will be encouraged to visualize their developing pregnancy on the
monitor and the provider will point out visible structures.

Women will be given feedback regarding the progression of the pregnancy and
reassurance if everything is progressing appropriately at each visit. They will also be
given time to ask questions and elicit advice applicable to the gestational age of the
pregnancy. Patients will be encouraged to bring their partner with them to visits. Partners
will be engaged during the visits through encouragement to visualize the pregnancy on
the ultrasound screen, involvement in conversations, and encouragement to ask questions.

Women in the TLC group will be seen by the same healthcare staff (medical
assistant and MD or PA) at each clinic visit. This continuity of care will promote the
formation of a trusting relationship between the patient and her healthcare providers and
help the patient feel as though the staff knows her. The goal of this continuity of care will
be to help women feel more comfortable attending the clinic during the first trimester.
Providers managing patients in the TLC group will be advised to exhibit empathy and
support when engaging with the women. They will be asked to address the emotional needs of the patients and listen to concerns that arise. A social worker will be available at the clinic if women feel as though they need to speak to someone further regarding their psychological and emotional well-being. The social workers will be available to provide counseling and support services if patients desire to utilize this component of TLC.

Women will be reminded of this resource at each visit.

Women in the TLC group will be advised to notify the clinic if they have concerns or experience bleeding during the first trimester. Women will be able to speak to their healthcare provider or come in for a visit if they so desire.

Women in the intervention group will also be asked to establish a relationship with their standard OB-GYN practitioner. They will be advised to notify their practitioner upon becoming pregnant and asked to follow their prenatal care instructions and appointment schedule. This will ensure that women in the TLC group receive standard prenatal care and aid in the continuity of care at the completion of the study intervention.

3.8 Comparison

Women randomized to the comparison group will be asked to attend the clinic of their standard OB-GYN practitioner for routine prenatal care. Women will be told to notify their OB-GYN upon becoming pregnant and asked to follow their prenatal care instructions and appointment schedule. They will be advised to notify their OB-GYN provider if they have any concerns regarding their pregnancy during the study period.

3.9 Adherence

Adherence to treatment in the intervention group will be monitored by recording the participants’ TLC office visits (Appendix G). If a patient misses an appointment, she
will be contacted by phone and the visit will be rescheduled accordingly. Adherence to treatment in the comparison group will be difficult, as patients will be released to the care of their standard OB-GYN. Women in the comparison group will be asked to give a self-report of their prenatal care at the completion of the study.

3.10 Study Variables and Measures

The following patient baseline characteristics will be collected and recorded on the form found in Appendix E: age category at randomization (18-24, 25-29, 30-34, or 35-39 years old), ethnicity (Hispanic or Latino, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White), marital status (married or not married), BMI category (normal weight: 18.50-24.99 kg/m^2 or overweight: 25.00-29.99 kg/m^2), known or unknown etiology for RPL, primary (no history of prior live birth) or secondary (history of prior live birth) RPL, and numerical category of previous losses (two, three, four, five, or six or more).

Pregnancy will be confirmed prior to randomization for treatment through the measurement of serum hCG. Women in both groups will be assessed for the presence of a clinical pregnancy, as visualized on transvaginal ultrasound, at five weeks of gestation. The primary outcome measure will be the presence of an ongoing viable pregnancy at 12 weeks of gestation, as visualized by transvaginal ultrasound.

Secondary outcome measures will include first trimester bleeding, ectopic and molar pregnancies, subsequent SAB, and the termination of pregnancy. In addition, psychological distress will be a secondary outcome measure. The Edinburgh Depression Scale (EDS) will be utilized to measure psychological distress (Appendix H). Women in both groups will complete the EDS when they present to the office for serum hCG
confirmation of pregnancy and when they present for assessment of clinical pregnancy status at 12 weeks.

3.11 Data Collection

Eligible women will undergo a history and physical exam following consent for study participation. Baseline characteristics will be collected at this time (Appendix E).

Each patient will have a data collection form to be kept under lock and key at her respective site (Appendix I). The form will include the patient’s ID, date of last menstrual period (for the calculation of gestational age), initial hCG, documentation of clinical pregnancy at five weeks of gestation, pregnancy outcome at 12 weeks, EDS scores, presence/absence of a multiple gestation pregnancy (pre- and post-intervention), adverse events, and establishment of routine prenatal care.

Study participants will be asked to notify their respective institution upon becoming pregnant. At this time they will present for the measurement of serum hCG by a medical assistant (MA). All women randomized to a study group will present for confirmation of clinical pregnancy at five weeks of gestation by transvaginal ultrasound. They will return at 12 weeks of gestation for the assessment of clinical pregnancy status. A clinician blinded to group assignment will perform these ultrasounds. Study participants will complete the EDS when they present for confirmation of pregnancy by hCG and when they present for assessment of clinical pregnancy at 12 weeks. A clinician blinded to group assignment will score the EDS (scoring scale found in Appendix H).

Another form will be utilized for women in the TLC group (Appendix G) to keep track of hCG and ultrasound monitoring visits, the patients’ utilization of resources, and additional visits or phone calls that patients make to their respective institution.
3.12 Monitoring of Adverse Events

Monitoring of adverse events will include first trimester bleeding, ectopic and molar pregnancies, subsequent SAB, and termination of pregnancy. Women will be asked to notify their healthcare providers if they experience first trimester bleeding. Women in the TLC group will contact their clinician at the study institution, and women in the comparison group will contact their standard OB-GYN. Ectopic pregnancies will be diagnosed by the absence of an appropriately rising serum hCG prior to the establishment of clinical pregnancy and the absence of an intrauterine pregnancy on ultrasound. Clinicians at the study institutions will manage molar and ectopic pregnancies and subsequent SABs in women assigned to the TLC group. Women in the routine prenatal care group will be managed by their OB-GYN clinicians. If a fetal anomaly is identified in patients in either group, and the couple desires to terminate the pregnancy, they will be referred to clinicians who can aid in management of the termination.

The EDS will be used to measure psychological distress. Women who score 12 or higher will be advised to notify their general practitioner or OB-GYN of their EDS score at the end of the study. The EDS is a screening tool and cannot be used for diagnosis. Patients scoring 12 and higher should undergo a clinical psychiatric evaluation.

3.13 Sample Size Calculation

We estimated that a sample size of 242 total patients, with 121 patients in each group, will be needed to test a two-sided hypothesis with a five percent confidence level and 80% power. A two-sample proportion calculation (Chi-square test) was utilized for the determination of the sample size via Version 4 of Power and Precision software.
Using data from prior studies, we estimated rates of successful pregnancy outcome (ongoing viable pregnancy at 12 weeks of gestation, as visualized by ultrasound) of 70% in the standard prenatal care group and 85% in the TLC group. The observation of an absolute 15% difference (effect size) in the rate of successful pregnancy outcome between the two groups requires a sample size of 121 patients per group (242 patients total). An estimated 10% loss to follow-up rate is expected and will be accommodated for by randomizing 267 patients for treatment in the study.

3.14 Statistical Analysis

The most recent edition of Statistical Analysis System software will be utilized for statistical analysis. The statistician will be blinded to group assignment. Probability values less than 0.05 will indicate statistical significance.

Baseline patient characteristics will be collected and compared between the two groups using descriptive statistics. Categorical variables (age category at randomization, ethnicity, and numerical category of previous pregnancy losses) and dichotomous variables (marital status, BMI category, known versus unknown etiology for RPL, and primary versus secondary RPL) will be compared between the groups by Chi-square tests.

The unadjusted association between TLC and successful pregnancy outcome at 12 weeks of gestation will be compared between the groups using the Chi-square test. Multivariate analysis will be performed using logistic regression, taking into account covariates. Covariates selected for multivariate analysis will be age category at randomization, numerical category of previous pregnancy losses, known vs. unknown etiology for RPL, and primary vs. secondary RPL. The primary outcome analysis will be
performed on an intention-to-treat basis. A sub-group analysis of women who achieve a clinical pregnancy will also be conducted to compare the association between TLC and successful pregnancy outcome between the intervention and comparison groups. This sub-group analysis will also exclude ectopic and molar pregnancies, terminations, and multiple gestation pregnancies.

A stratified analysis will be conducted to compare the association between TLC and successful pregnancy outcome at 12 weeks among women with a known etiology for RPL and women with an unknown etiology for RPL using an interaction term.

Comparison of secondary outcome measures of dichotomous variables operationalized by frequency, including first trimester bleeding, ectopic and molar pregnancies, SAB, and termination of pregnancy, will be performed by Chi-square tests.

The association between TLC and psychological distress will be measured using the EDS at baseline and post-intervention. The EDS will be scored using the scoring scale found in Appendix H. The difference between the baseline and post-intervention scores will be calculated (change score) and the difference in mean change scores between the two groups will be evaluated using the student’s t-test. Multivariate analysis will be performed using linear regression.

### 3.15 Timeline and Resources

Rolling basis recruitment will take place from January 1, 2015 to August 1, 2016. Women will be able to notify their institution of a pregnancy until September 1, 2016. This will ensure that all data collection can take place by mid-December, 2016. Data collection will end on December 31, 2016. The duration of the intervention will be from randomization following the confirmation of pregnancy by serum hCG through
pregnancy loss or assessment of pregnancy at 12 weeks of gestation by transvaginal ultrasound. Statistical analysis will take place after the completion of data collection.

Study personnel will include the study PI, Pinar Kodaman, MD, and co-PI, Emily Gruetzmacher, PA-SII. An institution PI will be assigned to each site. They will be responsible for recruiting and consenting eligible women for study participation. They will also communicate the randomization of study participants at each site and manage patient documentation and data forms. The institution PIs will be blinded to the randomization process. MAs and clinicians (MDs and PAs) working at each of the five institutions will be asked to participate in the study. Those who agree to participate will be identified and assigned patients upon patient randomization. The MAs will be responsible for all phlebotomy. Clinicians who agree to participate in providing patients with TLC will be asked to exhibit empathy and support to their patients, listen to questions and concerns, and address emotional needs. Clinicians not involved in the provision of TLC at each site will be needed to assess clinical pregnancy at five and twelve weeks of gestation and score the EDS at the beginning and end of patients’ study participation. These clinicians will be blinded to group assignments. A social worker will be needed at each site. In addition, the study will require an independent randomization coordinator and a statistician for data analysis. These individuals will not be involved in the recruitment or intervention phases of the study.

The study PI and co-PI will work from Yale School of Medicine. A workstation with a desk and a computer will be needed at each institution for the institution PI. Resources at each institution, such as exam rooms and ultrasound machines, will be utilized. Blood samples will be sent to and analyzed at labs associated each institution.
CHAPTER 4: CONCLUSION

4.1 Study Advantages

The proposed study will be a RCT examining the relationship between TLC and early pregnancy outcomes and levels of psychological distress in women with a history of early RPL. The study design is an important advantage of the study because it will minimize selection bias and the potential for confounding by ensuring that the two groups are equal with respect to baseline characteristics. Allocation concealment and utilization of a central randomization process will also aid in reducing selection bias.

Another strength of the study is adherence to a power of 80% and a significance level of 5% to generate statistically significant results. The sample size necessary for the study is achievable, considering the number of RPL patients that presented to Yale over a five-year period and the utilization of five institutions. It is reasonable to presume that a sufficient number of patients will present for enrollment during the recruitment period.

Women will only be eligible for study participation for one pregnancy. This is advantageous because the inclusion of more than one outcome from the same patient may skew the data, as pregnancy outcomes are often linked to maternal variables (such as age and number of previous losses). The proposed study will include women with both known causes for RPL and idiopathic RPL. The inclusion of both groups of women will give the study good external validity and make the results more generalizable to all women with a history of RPL. Finally, the utilization of two or more consecutive first trimester pregnancy losses as the definition for early RPL is important. This will aid in the recruitment of enough eligible participants. It is also advantageous because the diagnosis of an etiology for RPL does not differ in women with two versus three losses.
4.2 Study Disadvantages and Limitations

One of the main limitations of the proposed study is the difficulty of standardizing some aspects of the methods. Women in the comparison group will be released to their standard OB-GYN clinician for prenatal care. They will be seen by different clinicians and will receive variations of prenatal care. Clinicians vary in their interactions with patients and in their willingness to see patients for additional visits as concerns arise. In addition, clinicians providing TLC will be asked to exhibit empathy and support, listen to questions and concerns, and address the emotional needs of the patients. These qualities will naturally vary from clinician to clinician. Women in the intervention group will also have some control over the amount of care they receive. They will have the option of seeing a social worker at each visit and the availability of phone calls and office visits if concerns arise. This will cause variation in the amount of care that women receive.

Another disadvantage of the study is the potential costliness of TLC. The intervention will necessitate considerable planning and require staff trained in the management of RPL patients and the use ultrasound equipment. The intervention will require the availability of time for TLC appointments and office space. The dropout rate may be high in the intervention group due to the frequency at which patients must present for TLC. It is difficult to anticipate this, however, and it is likely that the patients will be highly motivated, as they will be recruited from reproductive clinics. This introduces another disadvantage: patients that present for care at these clinics may be homogeneous in terms of demographics and socioeconomic status, potentially limiting the study’s external validity. The feasibility of providing TLC to RPL patients in standard OB-GYN clinics will not be assessed and it may be difficult to replicate TLC in this setting.
The assessment of pregnancy outcome at 12 weeks of gestation, as opposed to the conclusion of pregnancy, may be viewed as a disadvantage of the study. The presence of an ongoing viable pregnancy at 12 weeks is a reasonable outcome measure, however, because most pregnancy losses occur during the first trimester. Patients with first trimester pregnancy loss will continue to lose during the first trimester.\textsuperscript{7-10}

Finally, the study may be influenced by recall bias. Women will be asked to report their number of previous losses and their experience of at least two clinically recognized first trimester losses. It may not be possible to verify this information.\textsuperscript{1}

4.3 Clinical Significance

Pregnancy loss is the most common adverse event of pregnancy and one to five percent of women experience RPL.\textsuperscript{11-13} The psychological implications of SAB and RPL can be severe, with symptoms of anxiety and depression sometimes continuing even after the birth of a healthy child.\textsuperscript{14} Psychological distress during pregnancy can negatively affect pregnancy outcomes and contribute to significant morbidity in offspring.\textsuperscript{15-17}

The proposed study will aid in determining if TLC does in fact influence pregnancy outcomes in women with RPL. The study will also assess the impact of TLC on levels of psychological distress in these patients. This information will provide the evidence and rationale for providing women with a history of two or more consecutive pregnancy losses with TLC. The study will also provide clinicians with a definition for TLC that outlines the components of care that are most effective and preferred by patients. A better understanding of the components of TLC and the relationship between TLC and pregnancy outcomes and psychological distress in women with RPL will guide clinical decision-making and patient management.
REFERENCES

Appendix A: Institution List

The proposed study will take place at the following institutions, all of which are associated with the Society for Assisted Reproductive Technology (SART).

CONNECTICUT:
The Center for Advanced Reproductive Services
The University of Connecticut Health Center
263 Farmington Avenue
Dowling South Building, 3rd Floor
Farmington CT 06030-6224
860-679-4580
Yale Reproductive Endocrinology and Infertility
150 Sargent Drive, 2nd Floor
New Haven, CT 06511
203-785-4708

 MASSACHUSETTS:
Brigham & Women’s Hospital Center for Assisted Reproduction
75 Francis St.
3rd Floor, ASB1-3
Boston, MA 02115
617-732-4222
Massachusetts General Hospital Fertility Center
32 Fruit Street
Yawkey Suite 10A
Boston, MA 02114
617-726-8868

NEW YORK:
Columbia University Center for Women’s Reproductive Care
1790 Broadway, Second Floor
New York, NY 10019
646-756-8282
Appendix B: Consent Form

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

Study Title: Tender Loving Care and the Woman with a History of Recurrent Pregnancy Loss
Principal Investigator: Pinar Kodaman, MD and Emily Gruetzmacher, PA-SII
Funding Source: To be determined

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the impact of increased first trimester care (tender loving care or TLC) on pregnancy outcome in pregnant women with a history of early first trimester recurrent pregnancy loss (RPL). You have been asked to participate because you are between the ages of 18 and 39 and you have a history of two or more consecutive first trimester clinical pregnancy losses. Approximately 267 pregnant women with RPL will participate in the study. The study will take place at five institutions within the Society for Assisted Reproductive Technology network.

The primary outcome of the study will be the presence of an ongoing viable pregnancy at 12 weeks of gestation, visualized by transvaginal ultrasound. Secondary outcomes include first trimester bleeding, ectopic and molar pregnancies, subsequent spontaneous abortion (miscarriage), and termination of pregnancy. Levels of psychological distress will also be assessed as a secondary outcome measure. Psychological distress will be measured using the Edinburgh Depression Scale (EDS) at the beginning and end of your participation in the study.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

1. If you consent to participate in the study, you will meet with a clinician who will ensure that you are eligible for the study. The clinician will ask you questions about demographics (age, ethnicity, etc.), your medical history, and your obstetric history. The clinician will also perform a physical exam.
2. If you remain eligible for participation in the study, you will be asked to contact the institution immediately upon becoming pregnant. At this time, you will present to the institution and a medical assistant (MA) will draw a small amount of blood to confirm that you are pregnant by the presence of a pregnancy marker in your blood called human chorionic gonadotropin (hCG). You will also be asked to complete the EDS at this time, which will serve as a measurement of your level of psychological distress.

3. Patients that become pregnant will then be randomly placed in two different groups by a computer-generated randomization system. One group will receive TLC during the first trimester of pregnancy and one group will receive standard prenatal care.

4. If you are randomly assigned to the TLC group, you will receive an increased level of prenatal care during the first trimester of pregnancy. This will include: frequent blood draws after a positive pregnancy test to ensure that the level of hCG is rising appropriately (this will occur until about the fifth week of pregnancy), weekly transvaginal ultrasounds from the fifth week of gestation until the twelfth week of gestation, continuity of care with the same medical staff at each visit to the clinic, reassurance regarding the progression of your pregnancy, and the availability of a social worker for counseling purposes at each office visit. You will be encouraged to bring your partner with you to your visits. At the beginning of the TLC care, you will receive a form outlining each of your visits to the office so that you know what to expect during the study intervention period. You will also be asked to notify your standard OB-GYN of your pregnancy to establish routine prenatal care.

5. If you are randomly assigned to the standard prenatal care group, you will be asked to notify your standard OB-GYN practitioner of your pregnancy. You will follow the prenatal care instructions and appointment schedule of your OB-GYN practitioner.

6. All women participating in the study will present to their respective institution at five weeks of gestation for a transvaginal ultrasound. This ultrasound will confirm the presence of a clinical pregnancy (a pregnancy that can be seen on ultrasound). All women will also return to the clinic at 12 weeks of gestation for another transvaginal ultrasound to assess pregnancy outcome, which will be the presence or absence of an ongoing viable clinical pregnancy. At this office visit, all women will be asked to complete another EDS to measure psychological distress.

7. Your participation in the study will end at the completion of the first trimester of pregnancy (12 weeks of gestation).

8. All information that is collected during the study that impacts your health will be reported to you and recorded in your medical record.

Risks and Inconveniences

We would like for you to be aware of some risks and inconveniences associated with this study. Participation in the study will require transvaginal ultrasounds, during which you may experience a small amount of discomfort. This should resolve immediately
following the exam and you will be able to return to your normal daily activities following your office visits. The transvaginal ultrasounds will not pose a threat to your developing pregnancy. Participation in the study will also require blood work, during which a very small amount of blood will be drawn. This may result in discomfort at the site of needle entry, bleeding, and the formation of a bruise.

**Benefits**

Participation in this study may result in a number of health benefits, including improved pregnancy outcome and a decreased level of psychological distress. In addition to the health benefits impacting you directly, this study may also benefit other women with a history of RPL by helping to define the most effective way to manage patients such as yourself and improve pregnancy outcomes.

**Economic Considerations**

During the study, you will receive routine prenatal care from your standard OB-GYN provider. You will be responsible for any co-pays required by your insurance company for the standard prenatal care. The additional prenatal care and testing that you may receive as a part of your participation in this study will be at no cost to you. You will be reimbursed for parking costs at the institution that you attend.

**Treatment Alternatives/Alternatives**

The alternative to participating in this study is declining to participate.

**Confidentiality**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. The study protocol will be in compliance with current Health Insurance Portability and Accountability Act (HIPAA) regulations. To protect the confidentiality of the study participants, all data from the study will be labeled with unique patient identification numbers. All identifiable patient information, including names, addresses, dates of birth, and medical histories will be kept secure. Records and study data will be kept in locked cabinets and on encrypted and password protected computers. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.
**In Case of Injury**

If you are injured as a result of your participation in the study, seek treatment and contact the study doctor as soon as you are able. Yale School of Medicine and Yale New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form.

**Voluntary Participation and Withdrawal**

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments. The researchers may withdraw you from participating in the research if necessary, for example if you experience an adverse pregnancy event, such as miscarriage, ectopic and molar pregnancies, or termination of pregnancy.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the Yale Fertility Center. The Yale Fertility Center will still treat you at your request or refer you to a clinic or doctor who can manage your care.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary, to insure the integrity of the study and/or study oversight.

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.
**Authorization**

_I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form._

Name of Subject: ________________________________

Signature: ____________________________________

Relationship: _________________________________

Date: ________________________________________

___________________________________________ ____________________
Signature of Principal Investigator Date

_or_

___________________________________________ ____________________
Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Pinar Kodaman, MD, or the co-PI, Emily Gruetzmacher, PA-SII, at (203) XXX-XXXX. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

**THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE HIC OFFICE**

**THIS FORM IS VALID ONLY THROUGH:**

______________________________________________
Appendix C: Letter to Study Institutions

Dear medical staff at (name of institution),

This letter is to inform you of an upcoming randomized controlled trial (RCT) assessing the difference in rates of successful pregnancy outcome at 12 weeks of gestation in women with a history of early recurrent pregnancy loss (RPL) who receive increased care (tender loving care or TLC) during the first trimester when compared with women who receive standard prenatal care during the first trimester. The study will take place at your institution and five other institutions within the Society for Assisted Reproductive Technology network.

RPL (the loss of two or more consecutive pregnancies) affects about one to five percent of couples. This is traumatic for many women and has significant psychological implications, which can persist even after the birth of a healthy child. Studies have shown that increased monitoring and support (TLC) from a dedicated team of healthcare providers during subsequent pregnancies can improve pregnancy outcomes in women with a history of RPL. Women with RPL also report that they want this increased care from their providers. Although the results of studies examining the impact of TLC on pregnancy outcomes in women with RPL are compelling, questions remain regarding the efficacy of TLC. In addition, the impact of TLC on levels of psychological distress in this patient population is not well understood. A RCT is needed to determine if TLC does in fact improve pregnancy outcomes in RPL patients by reducing the rate of spontaneous abortion (SAB) and if TLC has an impact on levels of psychological distress in this population.

Participant eligibility criteria:
Inclusion criteria:
- Women with a history of early RPL (two or more consecutive clinical pregnancy losses during the first trimester of pregnancy; clinical pregnancies are defined as pregnancies confirmed by ultrasound or histopathologic evaluation)
- Aged 18-39
- In patients with a history of prior live birth, the two most recent pregnancies must have ended in pregnancy loss
- Women with known and unknown etiologies for RPL (women with known etiologies may receive treatment prior to or during study enrollment; those with unknown etiologies must not be receiving empiric treatment)

Exclusion criteria:
- History of psychiatric illness
- Uncontrolled chronic disease (neurologic, cardiac, pulmonary, renal, and gastroenterology conditions)
- Uncontrolled endocrine disorders (diabetes and hypo-/hyperthyroidism)
- History of thrombophilia or venous thromboembolism
- BMI <18.50 kg/m² or ≥30 kg/m²
- Conception by in-vitro fertilization or artificial insemination
- Participation in another clinical study
Inability to abstain from tobacco and alcohol and consume less than 200 mg of caffeine per day during participation in the study

Patients that meet the eligibility criteria will be asked if they would like to participate in this study. Those who consent to participate will be screened through the completion of a baseline characteristics form and a physical exam. Those who remain eligible for the study will be asked to contact their respective institution upon becoming pregnant. At this time, women will present to the institution for confirmation of pregnancy through serum human chorionic gonadotropin (hCG) measurement. After pregnancy confirmation, women will be randomly assigned to receive TLC or standard prenatal care. TLC will include continuity of care from the same healthcare providers and serum hCG measurements every two days following a positive initial pregnancy test until a threshold of 2,000 mIU/ml or greater is reached. After that, TLC will include weekly transvaginal ultrasounds from five to twelve weeks of gestation, the availability of a social worker at each visit, and the involvement of each patient’s partner in the office visits. The primary outcome measure will be the presence or absence of a viable clinical pregnancy at 12 weeks of gestation, as visualized on transvaginal ultrasound. Women will also complete the Edinburgh Depression Scale (EDS) at the beginning and end of the study period. The EDS will be used to measure psychological distress in order to assess the impact of TLC on levels of psychological distress in patients with a history of RPL.

Your participation in this study will be greatly appreciated. We will need help with recruiting patients for the study. If you have patients that you think may be eligible for study participation, we ask that you notify your institution principal investigator (PI). We will need clinicians to provide TLC to participants in the study. We ask that these clinicians be willing to exhibit empathy and support when interacting with these patients during their TLC office visits. We will also need clinicians that are blinded to the study groups at each site to assess clinical pregnancy status by transvaginal ultrasound and score the EDS. A meeting will be held at your institution on (date) to provide the staff with more information and answer any questions. Please contact the study PI and/or co-PI if you have any questions or concerns (contact information below).

Thank you very much for your time and for considering involvement in this study. We look forward to working with you.

Sincerely,

Pinar Kodaman, MD
Principal Investigator
And
Emily Gruetzmacher, PAS-II
Co-PI

(203) XXX-XXXX
emily.gruetzmacher@yale.edu
Appendix D: Patient Flyer

Recurrent Pregnancy Loss

Research Study

If you are between the ages of 18 and 39 and have a history of early recurrent pregnancy loss (2 or more consecutive first trimester pregnancy losses), you may be eligible for participation in a clinical study.

We are studying the impact of increased first trimester care on pregnancy outcomes and levels of psychological distress in women with a history of early recurrent pregnancy loss.

Please contact the institution principal investigator at (name of institution) at (phone number) if you have more questions and/or would like to participate.

You may also contact the study PI, Pinar Kodaman, MD, or co-PI, Emily Gruetzmacher, PAS-II, if you have any questions or concerns.

(203) XXX-XXXX
Appendix E: Baseline Characteristics Form

Participant ID: _______________ Date: _______________

Age: _______________
Height: _______________
Weight: _______________

Physical Exam performed? Yes or No

Please circle the following:

Age category (TO BE COMPLETED AT RANDOMIZATION):
18-24 25-29 30-34 35-39

Ethnicity:
- Hispanic or Latino
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White

Marital Status:
- Married
- Not Married

BMI:
- Normal Weight (18.50-24.99 kg/m²)
- Overweight (25.00-29.99 kg/m²)

Known vs. Unknown Etiology for RPL:
- Known
- Unknown

Primary vs. Secondary RPL:
- Primary
- Secondary

Numerical Category of Previous Losses:
1 2 3 4 5 6 or more
Appendix F: TLC Form for Patients

Dear Study Participant,

You have been randomly assigned to the TLC group. A medical assistant (MA) and the scheduling staff at your institution will complete this form. All TLC office visits will be outlined below. Until about the fifth week of your pregnancy, you will come to the office every two days for blood samples to be drawn. This will monitor the hCG (pregnancy marker) in your blood to ensure that it is rising appropriately. Starting at week five of your pregnancy, you will come to the office once a week for a transvaginal ultrasound. At each office visit you will have the opportunity to ask questions or address any concerns that you might have. In addition, please take note of the following:

- You will see the same clinician (MD or PA) and MA at each of your appointments.
- Your partner is encouraged to come to each office visit with you to participate in the TLC care. Your partner will also have the opportunity to ask questions and engage in conversation.
- A social worker will be available at each visit. Please feel free to utilize this resource at any time if you so desire.
- Please notify your general OB-GYN practitioner of your pregnancy. Please attend appointments with them as scheduled and follow their advice regarding routine prenatal care.
- Please notify the office if you experience any bleeding or if you have any questions or concerns.

Thank you for your willingness to participate in this study. You will receive TLC until the completion of your first trimester of pregnancy (12 weeks of gestation).

To be completed by MAs and scheduling staff:

Your clinician: ____________________
Your MA: ____________________
Your social worker: ____________________
Office phone number: ____________________

Please see the reverse side of this form for your appointment dates.
hCG monitoring appointments (every 2 days following a positive pregnancy test until a hCG threshold of 2,000 mIU/ml or greater is reached):

<table>
<thead>
<tr>
<th>Date of Appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Transvaginal ultrasound appointments (from 5 weeks of gestation until 12 weeks of gestation):

<table>
<thead>
<tr>
<th>Gestational Week</th>
<th>Date of Appointment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix G: TLC Data Collection Form

Participant ID: ____________________

Participant’s clinician: ____________________
Participant’s MA: ____________________
Participant’s social worker: ____________________

hCG monitoring appointments:

<table>
<thead>
<tr>
<th>Date of Appointment</th>
<th>hCG Level</th>
<th>Did patient’s partner attend the visit? (yes or no)</th>
<th>Did patient see social worker? (yes or no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Transvaginal ultrasound appointments:

<table>
<thead>
<tr>
<th>Date of Appointment</th>
<th>Presence of Ongoing Viable Clinical Pregnancy?</th>
<th>Did patient’s partner attend the visit? (yes or no)</th>
<th>Did patient see social worker? (yes or no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Please record any additional patient phone calls or office visits below:

<table>
<thead>
<tr>
<th>Date of Call or Visit</th>
<th>Reason for Call or Visit (please indicate if patient called the office or physically visited the office)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix H: EDS and Scoring Scale

Edinburgh Depression Scale (EDS)

Patient ID: ______________________________

As you are pregnant, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

Here is an example, already completed.

- I have felt happy:
  - □ Yes, all the time
  - □ Yes, most of the time
  - □ No, not very often
  - □ No, not at all

This would mean: “I have felt happy most of the time” during the past week.

Please complete the other questions in the same way.
In the past 7 days:

1. I have been able to laugh and see the funny side of things:
   - □ As much as I always could
   - □ Not quite so much now
   - □ Definitely not so much now
   - □ Not at all

2. I have looked forward with enjoyment to things:
   - □ As much as I ever did
   - □ Rather less than I used to
   - □ Definitely less than I used to
   - □ Hardly at all

3. *I have blamed myself unnecessarily when things went wrong:
   - □ Yes, most of the time
   - □ Yes, some of the time
   - □ Not very often
   - □ No, never

4. I have been anxious or worried for no good reason:
   - □ No, not at all
   - □ Hardly ever
☐ Yes, sometimes
☐ Yes, very often

5. *I have felt scared or panicky for no very good reason:
☐ Yes, quite a lot
☐ Yes, sometimes
☐ No, not much
☐ No, not at all

6. *Things have been getting on top of me:
☐ Yes, most of the time I haven’t been able to cope at all
☐ Yes, sometimes I haven’t been coping as well as usual
☐ No, most of the time I have coped quite well
☐ No, I have been coping as well as ever

7. *I have been so unhappy that I have had difficulty sleeping:
☐ Yes, most of the time
☐ Yes, sometimes
☐ Not very often
☐ No, not at all

8. *I have felt sad or miserable:
☐ Yes, most of the time
☐ Yes, quite often
☐ Not very often
☐ No, not at all

9. *I have been so unhappy that I have been crying:
☐ Yes, most of the time
☐ Yes, quite often
☐ Only occasionally
☐ No, never

10. *The thought of harming myself has occurred to me:
☐ Yes, quite often
☐ Sometimes
☐ Hardly ever
☐ Never

Administered/Reviewed by ________________________________
Date ______________________________


Users may reproduce the scale without further permission providing they respect copyright by quoting the names of the authors, the title and the source of the paper in all reproduced copies.
Edinburgh Depression Scale (EDS)

SCORING:
Questions 1, 2, & 4 (without an *):
Are scored 0, 1, 2 or 3 with top box scored as 0 and the bottom box scored as 3.

Questions 3, 5-10 (marked with an *):
Are reverse scored, with the top box scored as a 3 and the bottom box scored as 0.

Maximum score: 30
Possible Depression: 10 or greater
Always look at item 10 (suicidal thoughts)

Instructions for using the Edinburgh Postnatal Depression Scale:
1. The mother is asked to check the response that comes closest to how she has been feeling in the previous 7 days.
2. All the items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others. (Answers come from the mother or pregnant woman.)
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.


Users may reproduce the scale without further permission providing they respect copyright by quoting the names of the authors, the title and the source of the paper in all reproduced copies.
Appendix I: Patient Data Collection Form

Participant ID: __________________________

Data of Last Menstrual Period: ______________________
Estimated Gestational Age at Initial hCG Visit: ______________________

Initial hCG (confirmed pregnancy – positive or negative): ______________________

Presence or Absence of Ongoing Viable Clinical Pregnancy at 5 Weeks of Gestation:
  Yes       No

Presence or Absence of Ongoing Viable Clinical Pregnancy at 12 Weeks of Gestation:
  Yes       No

EDS Score at Beginning of Study Period: ______________________

EDS Score at End of Study Period: ______________________

Multiple gestation pregnancy:
  Yes       No

Adverse Events (circle):
  • First Trimester Bleeding
  • Ectopic Pregnancy
  • Molar Pregnancy
  • Subsequent SAB
  • Termination of Pregnancy

Did patient establish routine prenatal care with her standard OB-GYN clinician? (circle)
  Yes       or       No
Appendix J: Sample Size Calculation

Calculated using Power and Precision, Version 4

<table>
<thead>
<tr>
<th>Group</th>
<th>Proportion Positive</th>
<th>N per Group</th>
<th>Standard Error</th>
<th>95% Lower Limit</th>
<th>95% Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Prenatal Care</td>
<td>0.70</td>
<td>121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLC</td>
<td>0.85</td>
<td>121</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate Difference</td>
<td>-0.15</td>
<td>242</td>
<td>0.05</td>
<td>-0.25</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

Alpha = 0.050, Tails = 2, Power = 0.802
Power computation: Normal approximation (unweighted mean p)
Precision computation: Log method
BIBLIOGRAPHY


