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Examining the roles of pregnancy intention and perceived infertility risk on preconception health behaviors to optimize pregnancy among female survivors of adolescent and young adult cancers

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Health Behavior)

by

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The Dissertation of Hena Naz Din is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

I dedicate this dissertation first to Allah in gratitude for the blessing of knowledge and for the opportunity to contribute to meaningful scholarship, and second to my family:

to my parents, Ahmed and Naz, who grew my confidence and who's duas (prayers) guided me,

to my loving husband, Atif, who encouraged me to the finish line,

to Shabana and Omar, who inspired me and paved the way for me,

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and to my little Layla for her happy giggles when I needed it most,

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LIST OF ABBREVIATIONS

AMH, Antimüllerian hormone

aOR, Adjusted Odds Ratio

AYA, Adolescent and Young Adult

BMI, Body Mass Index

CED, Cyclophosphamide Equivalent Dose

CI, Confidence Interval

DBS, Dried Blood Sample

ELISAs, Enzyme-Linked Immunosorbent Assays

FSH, Follicle-Stimulation Hormone

GLMM, Generalized Linear Mixed Effects Model

HBM, Health Belief Model

LMM, Linear Mixed Effects Model

LMUP, London Measure of Unplanned Pregnancy

MAR, Missing at Random

MI, Multiple Imputations

MICE, Multiple Imputation Chain Equation

OKQ, One Key Question

OR, Odds Ratio

PA, physical activity

PIS, Pregnancy Intention Score

RCAC, Reproductive Concerns After Cancer

SD, Standard Deviation

WINDOW, Reproductive Window in Young Adult Cancer Survivors Study

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ABSTRACT OF THE DISSERTATION

Examining the roles of pregnancy intention and perceived infertility risk on preconception health behaviors to optimize pregnancy among female survivors of adolescent and young adult cancers

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Background: Fertility and family planning are key areas of focus for adolescent and young adult (AYA) cancer survivors. Pregnancy intention is associated with preconception health behaviors in general populations of women, but few studies explored the role of intention among female AYA survivors.

Aims: This dissertation aimed to evaluate: 1) associations between pregnancy intentions and preconception health behavior (specifically: physical activity (PA), cigarette smoking, and alcohol consumption), 2) potential moderation by perceptions of post-cancer treatment infertility risk on preconception health behavior, and 3) factors associated with infertility risk perception and risk estimation.

Methods: Data for this dissertation came from participants of the Reproductive Window in Young Adult Cancer Survivors (Window) study, a longitudinal study to estimate the trajectory of ovarian function among AYA survivors. Participants were followed for 1.5 years encompassing 4 data collection time points from baseline and every 6 months. Study #1 utilized baseline data to evaluate associations between pregnancy intentions and preconception behavior with regression analysis. Study #2 utilized data from all time points to estimate the association between changing pregnancy intentions and preconception behavior with longitudinal mixed effects models. Both Study #1 & #2 evaluated potential effect modification by infertility risk perception. Study #3 utilized baseline surveys, medical chart abstracted treatment information, and biomarkers collected to measure ovarian reserve. Multivariable logistic regressions evaluated associations with perceived infertility risk and with risk estimation between perceived and objective infertility risk.

Results: Study #1 and #2 found urgent pregnancy intention was associated with higher preconception PA. In Study #1 survivors with higher pregnancy intention and perception of infertility risk reported higher PA compared to survivors who did not perceive infertility risk. In Study #3 experiencing either higher gonadotoxic cancer treatment or amenorrhea was associated with higher odds of infertility risk perception. Poor agreement (κ =0.19) was found between perceived and objective infertility risks.

Conclusions: This dissertation provided insight into the role of pregnancy intention on preconception health behavior and identified factors that may inform perceived infertility risk. Knowledge gained from this dissertation may guide behavioral interventions targeting female AYA survivors and inform infertility risk education needed within survivorship care.

CHAPTER 1

Introduction

DISSERTATION THEME AND AIMS

The theme of this dissertation was to evaluate the relationships of pregnancy intention and perceived infertility risk on select preconception health behaviors (specifically: physical activity, smoking, and alcohol consumption) among a sample of reproductive-aged, female adolescent and young adult (AYA) cancer survivors. Two of the dissertation manuscripts focused on pregnancy intentions and perceived infertility risk (as a moderator) and how they relate to preconception health behavior. The last manuscript characterized infertility risk perception.

- Study #1 Aim: To determine the association between pregnancy intention and engagement in preconception health behaviors (i.e., smoking, alcohol consumption, and physical activity) among AYA cancer survivors. To determine the role of perceived infertility risk in the association between intention and behavior.

- Study #2 Aim: To examine the role of changing pregnancy intentions on preconception health behaviors (i.e., smoking and physical activity) longitudinally. To determine the role of perceived infertility risk in the association between intention and behavior over time.

- Study #3 Aim: To evaluate the association of treatment gonadotoxicity and menstrual pattern with infertility risk perception among female AYA survivors. To evaluate the agreement between infertility risk perception and objective ovarian function.

Taken together, this dissertation sought to discover 1) where pregnancy intentions may relate to preconception health behavior, 2) if perceptions on post-cancer treatment infertility risk were associated with varying engagement in preconception health behavior, and 3) what factors informed infertility risk perception and are associated with to discordant estimation.

BACKGROUND

AYA cancer is diagnosed between the ages of 15-30.[1–3] An estimated 70,000 AYAs are diagnosed with cancer each year, with a higher proportion of females (>45,000) diagnosed than males.[4,5] AYAs experience cancer at an 8-fold higher incidence than children, and AYA cancers account for 5% of all cancers diagnosed in the U.S.[4,6] Female AYAs commonly experience thyroid, lymphoma, leukemia, and melanoma cancers.[6] Survivorship care is of great importance for AYA's as 5-year survival rates have increased to 86%, and more survivors are in need of long-term follow-up and guidance.[7]

AYA cancer care falls in between pediatric and adult care without its own niche that addresses AYA's unique developmental needs.[8] During this period they are transitioning from pediatric care, largely overseen by their parents/ guardians, to adult care navigated on their own.[6] Cerebral maturity for decision-making and life navigation are still developing until at least till 30 years of age, which impacts diagnoses comprehension and treatment adherence among AYAs.[6] AYAs cared for in both pediatric and adult settings are understudied in both clinical trials and patient outcome studies. This is a disadvantage to AYAs who are needed in both types of studies to improve treatment options and care.

Risk of infertility causes significant anxiety and uncertainty in many female cancer survivors.[9] Cancer treatments are known to cause infertility via injury to gonads, disruption of hypothalamic-pituitary-gonadal function, and/or injury to the uterus.[10] Clinical infertility is defined as the inability to become pregnant after more than 1 year of trying.[11] Treatments like surgical removal/ alteration of reproductive organs, chemotherapy (especially alkylating agents) and radiation (total body and specific areas) are all associated with risk of infertility.[11,12] Fertility preservation is a significant topic for AYAs diagnosed with cancer, because of the risks to fertility posed by treatments. In a study among breast cancer survivors, participants described feeling inadequately informed on fertility risks and options on preservation. This was compounded with feeling rushed to begin treatment and lack of insurance coverage for some options.[13,14] Survivors often desire having children years after cancer diagnosis driven by a

number of reasons including the importance of parenthood, the desire to maintain normalcy after cancer, and/or the desire to be optimistic.[1,15] Infertility rates are higher among AYA cancer survivors (15-27%) when compared to childhood cancer survivors (13-16%).[1,11] A study comparing childhood and AYA cancer survivors to their siblings found AYA survivors were 50% less likely to have a child because of infertility.[16] AYA cancer survivors experience lower rates of pregnancies and live births, and increased risk of adverse neonate outcomes.[17] These risks highlight the importance of the preconception period for female AYA cancer survivors and the need for engagement in positive health behaviors and medical guidance.

The preconception period, from a life course perspective, is the total years a woman has lived till she becomes pregnant.[18–20] The life course perspective considers a cumulative effect over time of overall health and lifestyle behaviors of women on their reproductive health.[20] This perspective incorporates women who have formalized an intention to become pregnant as well as women who have no intention, or ambivalent intention, to become pregnant but are of reproductive age and engage in sexual activity.[18] Health behaviors during preconception can affect ability to become pregnant, child development in utero, and post-birth outcomes. Key preconception health behaviors include regular physical activity, healthy weight maintenance, ceasing smoking and alcohol consumption, folic acid supplementation, not delaying pregnancy later in life, and seeking medical guidance when necessary.[21,22] This study will focus on three behaviors: smoking, alcohol use, and physical activity.

Smoking. Cigarette smoking has been associated with lowered rates of fertility among women and men.[23] A population cohort study showed fertility rates were reduced for women among current, former and occasional smokers.[24] Preconception smoking can impact maternal and neonate health, for example smoking is a major risk factor for tubal ectopic pregnancies and is also associated with approximately 3 times higher risk of congenital heart defects in neonates.[23,25] Maternal smoking is also associated with adverse neonate outcomes like low-birth weight, prematurity, and sudden infant death syndrome.[26]

Alcohol Consumption. A meta-analysis of alcohol consumption before and during pregnancy found a dose-response between maternal alcohol consumption and low-birth weight, preterm birth, and small for gestational age outcomes.[27] Alcohol exposure prenatally is also associated with poor cogitative and behavior outcomes in children.[28] Preconception binge drinking may lead to a 20% increase in risk of neural tube defects when compared to low levels of drinking.[25] Preconception drinking is also associated with a 30% increase in spontaneous abortions although this increase is not significant.[25]

Physical Activity. Pre-pregnancy vigorous physical activity and brisk walking were shown to be protective against gestational diabetes when compared to inactivity. [29] Preconception physical activity is associated with lowered risk of excessive weight gain during pregnancy.[30] Obesity and a less active lifestyle are associated with complications conceiving, gestational diabetes, and neonate outcomes like low birth weight and congenital anomalies.[20,29]

AYA cancer survivors are known to engage in unhealthy behaviors even though they are at higher risk for chronic illnesses and are advised to maintain healthy lifestyles.[31–33] Multiple studies have shown that a high proportion of cancer survivors smoke.[34] In a population study, female AYA cancer survivors were significantly more likely to smoke (27-29%) compared to females of similar demographics but without cancer (14-18%).[31,35] Additionally, an estimated 13.1% of AYA survivors reported binge drinking.[35] This is not significantly different from the general population, but alcohol consumption is discouraged for cancer survivors because of harmful effects that may increase the risk of a second cancer.[36,37] Although further research is needed regarding physical activity among AYA cancer survivors, current knowledge indicates that physical activity significantly declines during treatment and remains low post-treatment.[32,35,38,39] Physical activity in cancer survivors has been shown to improve quality of life and improved survival.[32,38] No studies were identified that specifically assessed smoking, alcohol consumption, and physical activity behaviors during preconception among AYAs, but given the above evidence, there is a need to understand preconception health behaviors among AYA

survivors. Health behavior and life course theories posit that engagement in preconception health behaviors may be influenced by constructs like intention, time to intention completion, and perceived threats/ complications to achieving a pregnancy.

THEORTICAL FRAMEWORK

The Rubicon Action model describes the process of intention formation and the mental timeline that often comes with wanting to achieve an intention or goal.[40] The Rubicon model argues that motivations and actions before an intention is formed (pre-decision) versus after, are different because of the formation of the intention.[40] Once an intention is formed, an individual is either in a non-urgent action phase, meaning they have no immediate plans to reach their goal deadline or they are in an urgent action phase (immediate intention).[41] In the context of pregnancy, those who have formed a pregnancy intention may engage in behavior that increases the likelihood of conceiving, compared to women who have no pregnancy intention.[42] Pregnancy intention is not a dichotomous variable however, (presence of intention vs. no intention) and is known to have many dimensions. Most common dimensions include: planning, trying, wanting, attitude, and timing. Want is defined as some preconception desire to have a child without any specific details outlined.[43] Planning includes preconception desire and some level of intended action or actual action to initiate and or prepare for a pregnancy. Steps can include changes to personal health (improving diet), discussions with partner, and deciding when to cease birth control use.[43,44] Trying is a measure of behaviors, it focuses on actual steps taken to achieve a pregnancy and is usually more immediate (i.e. trying now.)[43] Attitude captures an important aspect of pregnancy intention which is positive, negative, or ambivalent affect when thinking of a pregnancy.[44] Most studies have assessed this dimension in retrospect (i.e., were you happy when you found out you were pregnant.)[44] Timing is also a dimension assessed in retrospect; it captures the alignment of the intended time of a pregnancy to the actual timing of the pregnancy. Generally pregnancies that occur in <2 years than when was

intended are labeled as seriously mistimed.[43,45] If a woman became pregnant after she intended, this pregnancy is not considered mistimed but rather a planned and wanted pregnancy.[43]

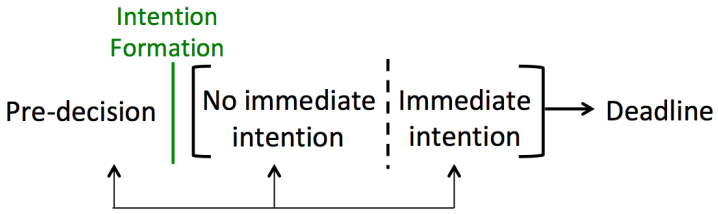

Figure 1.1 Overview of Rubicon Action Model

These dimensions represent a spectrum of pregnancy intention that represents different levels of effort and seriousness.[44,46,47] For example, wanting a baby may represent a different level of intention than trying to have a baby or planning to have a baby.[47] Studies indicate that each dimension is distinct and is associated with varied pregnancy outcomes. For example, unwanted and unintended pregnancies have both been associated with higher odds of pre-term birth but not mistimed pregnancies.[46,48] Per the Rubicon action model and the purposes of this dissertation, a spectrum of pregnancy intention will be utilized except with regards to *trying.* As described in Chapter 2, *trying* does not measure the same latent concept as *wanting* and *planning* do. *Trying* seems to be capturing a more urgent intention and thus may have a greater likelihood of being associated with behavior.

Another component that contributes to the formation of pregnancy intention is perceived infertility risk.[49] Perceived susceptibility of a health outcome is a specific determinant of behavior outlined in the Health Belief Model (HBM). Specifically, the HBM posits that individual belief's about an illness impacts their behaviors around that illness.[50] Individual belief's include many factors like perceived severity of an illness, likelihood of contracting/ developing an illness, and benefits in engaging in actions that would deter an illness.[50] The HBM details how perceived susceptibility to infertility may have significant impacts on preconception behavior.[21] This is

especially true among a population of cancer survivors who may perceive themselves at a higher infertility risk. The HBM predicts that individuals who want to get pregnant and who feel a higher infertility risk are more likely to engage in behaviors that will mitigate that risk.[21,50] Behaviors may include preconception health behaviors, seeking assisted reproductive technology treatment, and or considering surrogacy.

DISSERTATION OUTLINE

This dissertation is composed of an introduction (Chapter 1), three distinct manuscripts (Chapters 2 through 4) and a discussion (Chapter 5). Chapter 1 describes the background and significance as well as the theme and objectives of the dissertation. The first manuscript (Chapter 2) assessed the relationships between pregnancy intention, perceived infertility risk, and preconception health behaviors guided by the theoretical framework. Chapter 3 (the second manuscript) investigates the strength of the relationships detailed in Chapter 2 in the context of changing pregnancy intentions in a longitudinal analysis. The third paper (Chapter 4) is a cross-sectional exploration of the factors associated with infertility risk perceptions and characterized the agreement between perceived and objective infertility risk (measured by gondatoxicity of treatments, menstrual pattern, and biomarker samples of ovarian reserve). The final chapter (Chapter 5) includes a discussion of the key findings and suggestions for future research and/or clinical care recommendations.

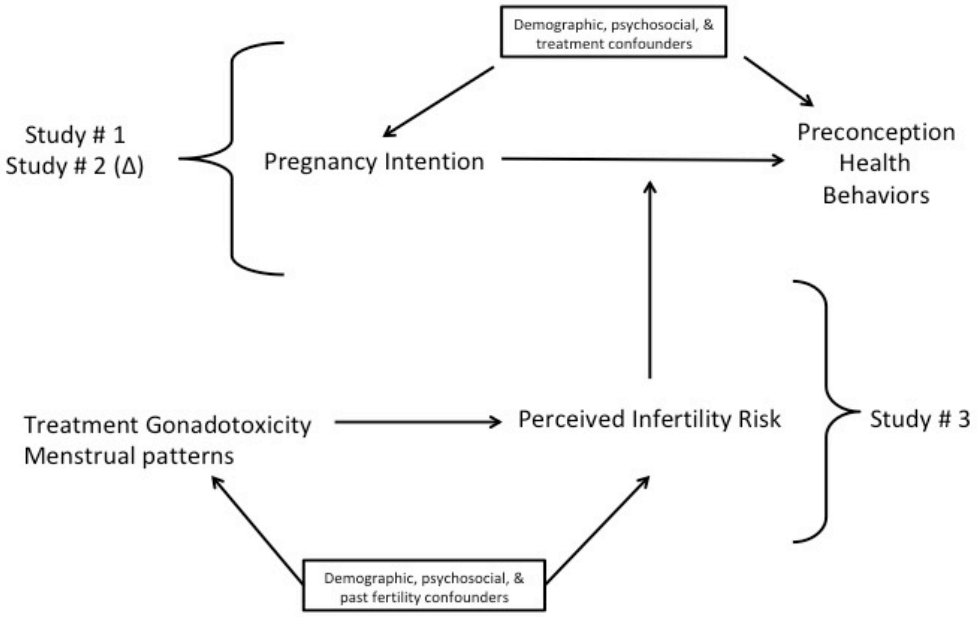

Figure 1.2. Overall diagram of dissertation project and corresponding studies.

STUDY POPULATION

All studies were conducted on data collected from participants recruited and consented to the Reproductive Window in Young Adult Cancer Survivors (Window) study. The Window study was a longitudinal study to estimate the trajectory of ovarian function among AYA survivors.[51] Participants were recruited between 2013-2017 and then followed for 1.5 years encompassing 4 data collection time points from baseline and every 6 months thereafter. Eligibility criteria included females 18-39 years old, diagnosed with AYA cancer between 15-39 years of age, completed primary cancer treatment, and had at least one ovary. Exclusion criteria were uncontrolled endocrinopathies and multiple cancers or recurrence. More than 30,000 recruitment letters were sent to potentially eligible individuals identified by the California and Texas cancer registries, social media, and physician referrals. Of this group n=1825 contacted the study team and were assessed for eligibility, 1269 were eligible, and 1159 consented to the study. A total of 1071 eligible participants completed baseline surveys and were included within the Window study.

Study #1 and #3 utilized baseline Window data; Study #1 utilized baseline surveys and Study #3 utilized baseline surveys, treatment details abstracted from medical charts, and biomarker results collected from participants through dried-blood collection methods. Study #2 utilized data from all surveys collected at each of the 4 timepoints. Study #2 only focused on smoking and physical activity preconception behaviors because participants were asked to report their alcohol consumption in the last 12 months whereas pregnancy intention was asked at present at each 6-month time point. A longitudinal analysis could not be conducted on an outcome (alcohol use) that occurred before an exposure (pregnancy intention).

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CHAPTER 2

Association between pregnancy intention and preconception health behaviors to optimize pregnancy among female survivors of adolescent and young adult cancers

ABSTRACT

Background. Female adolescent and young adult cancer survivors (AYA survivors) face higher infertility and pregnancy risks compared to peers with no cancer history. Preconception health behaviors like physical activity (PA], tobacco smoking, and alcohol intake influence reproductive outcomes. In general populations, pregnancy intention is positively associated with healthy preconception behaviors, but has not been studied among AYA survivors. We hypothesized higher pregnancy intention is associated with healthier behaviors, especially among AYA survivors with perceived infertility risk.

Methods. Cross-sectional analysis was conducted with data collected between 2013-2017 from 1071 female AYA survivors aged 18-39 years, who completed primary cancer treatment and enrolled in an ovarian function study. Self-reported intention dimensions were measured as a pregnancy intention score (PIS) and trying now to become pregnant. Multivariable linear (PA), binary (smoking), and ordinal (alcohol use) logistic regressions were used to estimate associations between intentions and preconception behaviors, adjusting for demographic and cancer characteristics. Effect modification by perceived infertility risk was assessed.

Results. Mean PIS was 1.1 (SD=0.77) on a 0-2 scale (2=high intention) and 8.9% were attempting pregnancy now. Higher PIS was associated with increased PA (β [95%CI]: 0.08[0.11,1.04]), while ambivalence in pregnancy intention was associated with lower alcohol consumption (Odds Ratio [95%CI]: 0.72[0.55,0.95]). Pregnancy intentions were not associated with smoking. Perceived infertility risk strengthened the relationship between PIS and PA ($p<0.05$).

Conclusions. Pregnancy intentions were associated with some healthier preconception behaviors in AYA survivors. Medical professionals caring for AYA survivors may consider pregnancy intention screening to guide conversations on preconception health.

INTRODUCTION

Reproductive-aged survivors of cancers diagnosed during adolescent and young adult years (AYA survivors) are a growing group with diverse and complex reproductive needs. An estimated 60% of female AYA survivors report the desire to have children in the future; however, many cancer treatments have adverse effects on fertility and pregnancy health.[1] Female AYA cancer survivors experience a 1.30-fold increase in diagnosed clinical infertility and a 39% decrease in pregnancy rates compared to peers with no history of cancer.[2,3] Cancer survivors are at higher risk of preterm birth (1.5-2-fold increase), low birth weight (2-3-fold increase), and pregnancy loss (1.4-2.8-fold increase) compared to pregnant women without prior cancer.[4] Given increased risks to fertility post-cancer treatment, engaging in healthy preconception behaviors may be particularly important for female AYA survivors.

Preconception health behaviors can affect fertility, pregnancy and neonatal outcomes but studies show AYA survivors engage in risky behaviors.[5] Healthy preconception behaviors like engaging in physical activity (PA) at recommended guidelines can be protective against excessive weight gain and gestational diabetes, while risky behaviors like smoking and high alcohol consumption are associated with reduced fertility, higher likelihood of unintended pregnancies, and adverse neonatal outcomes.[6–9] AYA survivors are less physically active, have higher rates of smoking and drink alcohol at similar rates compared to peers without cancer.[10,11] Poor health behaviors in AYA survivors are concerning because they may adversely impact already increased reproductive risks.

Pregnancy intention is positively related to healthy preconception behaviors in the general population,[12,13] but this relationship has not been studied in AYA survivors.[10,11] Health behavior change theories posit that engagement in preconception health behaviors may be influenced by intention and perceived threats to achieving a healthy pregnancy. Intention is associated with action as per the Rubicon Action model which details the process of intention formation as: no intention formed, non-urgent intention, and urgent intention.[14] The progression of intention formation is associated with increasing action.[14] Applied to preconception behaviors, dimensions of pregnancy intention like wanting a child, planning a pregnancy, and trying to become pregnant may lead to different levels of action. *Wanting* is preconception desire to have a child without any specific action outlined.[15] *Planning* includes preconception desire and incorporates some level of intended and real action to initiate or prepare for a pregnancy.[15,16] *Trying* represents urgent intention and focuses on real action taken to achieve a pregnancy, such as engaging in healthy preconception behaviors.[15] In addition, the Health Belief Model's (HBM) construct of perceived susceptibility may moderate the association between pregnancy intention and health behaviors, as those who perceive increased infertility risk due to gonadotoxicity of cancer treatments, may be more likely to engage in behaviors that will mitigate risk.[13,17] Guided by Rubicon's Action Model and the HBM, the objective of this study was to evaluate the association between pregnancy intention and engagement in PA, smoking, and alcohol use among female AYA survivors. It is hypothesized that higher levels of pregnancy intention will be associated with engagement in healthier preconception behaviors, especially among those with perceived infertility.

METHODS

This cross-sectional study used baseline data collected between 2013-2017 from the Reproductive Window in Young Adult Cancer Survivors study, a longitudinal study to estimate the trajectory of ovarian function among AYA survivors.[18] Participants were recruited through

California and Texas cancer registries, social media, and physician referrals. Eligible participants included females, 18-39 years old, diagnosed with cancer between 15-39 years of age, completed primary cancer treatment, and had at least one ovary. Exclusion criteria were uncontrolled endocrinopathies and multiple cancers or recurrence. For this analysis, participants who completed baseline surveys and had a uterus were included. All variables were self-reported via an online questionnaire.

Measurements:

Pregnancy intention dimensions. Three items captured the dimensions of *wanting, planning,* and *trying;* wanting and trying measures are from the U.S. National Survey of Family Growth.[19] On wanting, participants were asked if they would want a baby sometime in the future.[19] Final responses were *want* and *do not want* a child.

On planning, one item asked when participants plan on having a baby. To reflect a separation of urgent vs. non-urgent intention,[14] responses were collapsed into not planning (*not planning on having a child),* planning now (*already trying or will try in ≤ 1 year)*, and planning later (*between 1-to >5 years from now),* excluding *prefer not to answer*.

On trying, one item asked participants if they are attempting to become pregnant. Responses included *yes-trying now*, *no-avoiding pregnancy,* and *neither trying nor avoiding pregnancy*. *Neither* represented ambivalent intention.

The *wanting* and *planning* scales were summed to create a novel Pregnancy Intention Score (PIS), coding each item in a ranked manner, and subject to Mokken analysis.[20] Mokken analysis determines if items of different measures are scalable and work well together as a comprehensive measure.[20] Mokken analysis confirmed PIS was a robust scale with both a high *h* statistic of 0.85 and no violation of monotonicity.[20] The resultant PIS measured pregnancy intention on a 5-point scale from 0-2 with 2 representing highest intention. Because PIS was

created by summing a 2-point scale with a 3-point scale, ½ points were utilized to allow for equal weighting in the combination of the scales. *Trying* was kept separate as a dimension because when combined with the other dimensions of intention, monotonicity of the scale was violated. For final analyses, pregnancy intention was measured by two variables: PIS and *trying*.

Current smoking behavior. Participants were asked if they currently smoke tobacco with final responses as: *current smoker* (includes *daily* and *less than daily*) and *non-smoker*. [21] *Don't know* responses were excluded from analysis.

Physical activity. Participants were asked how many days they were physically active in the past 7 days for at least 30 minutes/day, including PA that increased heart rate and breathing.

Alcohol consumption. Participants reported the frequency of alcohol intake as the number of occasions any type of alcoholic drink/s was consumed in the last 12 months. Final categories included: Non-drinkers (never drank or did not drink in the last 12-months), occasional (*1-11x/ past year* or *1-3x/month*), and heavy (*1x/ week or more).*

Perceived infertility risk. Participants were asked if they felt their own fertility was greater, same, or less than their female peers.[22] Responses were collapsed to compare any perception of increased risk to no perception of increased risk. Per the HBM, any increase in risk may mitigate behavior.[17] Final categories were: *no increased risk* (includes greater or same level of fertility) and *increased risk* (includes less fertile or infertile).

Confounders. Due to limited research on preconception behaviors among AYA survivors, covariates described here were selected based on studies among general

populations of women that showed confounding. Demographic covariates included age, race, ethnicity, sexual orientation, education, income, marital status, and health insurance coverage. Respondents ranked their overall general health with 5 responses from excellent to poor. Body mass index (BMI) was calculated with self-reported weight and height. Self-reported comorbidities were categorized as cardiovascular/pulmonary, endocrine, psychological, and other comorbidities. Additional covariates identified as potential confounders included parity and cancer type and consultation with a fertility specialist before, during or after cancer treatment. Psychosocial factors included stress measured by the perceived stress scale-10 scale[23], depression measured by the patient health questionnaire depression scale[24], and social support by RAND institutes medical outcomes study survey.[25]

Statistical Analysis:

Independent variables were PIS and *trying* to become pregnant. Outcomes were days of PA in the last week, current smoking behavior, and alcohol consumption in the last year. Following descriptive analysis, bivariable analyses estimated associations between independent variables and outcomes using chi-square, Fisher's Exact and Student's t-test, as appropriate. Covariates closely associated with one another (Rho >=0.5) were reduced to include one of the two variables in the final model; age at enrollment, stress, and perceived infertility risk were retained in all multivariable models, while age at diagnosis, depression and type of cancer were not. For multivariable analysis, linear regression was utilized for PA given its approximate normal distribution, binomial logistic regression for smoking, and ordinal logistic regression for alcohol consumption. Each model was built from an explanatory model perspective. All covariates were included and then reduced if non-significant in the model and did not present confounding (≤ 10% change in parameter). Perceived infertility risk was assessed as a moderator in each final parsimonious model, in order to study whether the relationship between

pregnancy intention and outcome differed by perceived infertility risk. All analyses were conducted with R Studio Version 1.2.5001.

RESULTS

Sample Characteristics

A total of 1071 female AYA survivors were included (Table 1). Mean age (standard deviation [SD]) at study enrollment and at cancer diagnosis was 33.3 [4.9] and 25.7 [5.8] years, respectively. Majority of participants were non-Hispanic white (60.5%), married (68.8%), had a college education or higher (71.2%), and did not have a child (57.1%). The most common cancers included blood/leukemia (34.9%), breast (22.8%), and skin cancer (18.6%), which is similar to the general AYA population.[26] Majority of participants (63.3%) perceived themselves to be at higher risk of infertility and only 28% of participants had ever visited a fertility specialist. Overall mean PIS (SD) was 1.1 (0.77) with the most common response being participants wanted a child but were planning later (38%) (Table 2.) Additionally, 8.9% reported they were trying now to become pregnant while approximately 35% were ambivalent about pregnancy (Table 2.) Higher pregnancy intention was seen in participants of younger age, heterosexual orientation, in a partnered relationship, higher perceived infertility risk, and visited a fertility specialist (Supplemental Table).

Outcomes of Interest:

Physical activity. Participants reported a mean [SD] of 4.1 [2.0] days of PA in the last 7 days. In unadjusted and adjusted models (Table 3), PIS was not associated with PA, while those reporting *trying now* had higher levels of PA compared to participants *not trying* (adjusted β [95%CI]: 0.08 [0.11, 1.04]). Higher education, increased BMI, worse general health and moderate stress (compared to no/low stress) were associated with lower PA in both models.

Current smoking behavior. The majority of participants were not current smokers (93.9%). In unadjusted models (Table 4), higher PIS score was associated with lower odds of smoking, while ambivalent intention was associated with higher odds than those *not trying*. Neither association remained significant within adjusted models. Higher household income, parity, having health insurance, and more social support were found to be related to higher odds of smoking in both adjusted models.

Alcohol consumption. Half of participants reported occasional alcohol consumption in the past year (50.9%), with 38.6% reporting heavy consumption. In unadjusted models (Table 5), higher PIS was associated with higher odds of heavier consumption, while ambivalent intention was related to lower odds than those *not trying*. In adjusted models, only participants reporting ambivalent intention had significantly lower odds of heavy alcohol consumption compared to those not trying to be pregnant (OR 0.72 [0.55-0.95]). Non-White race, parity, and worse general health were associated with lower odds of heavy alcohol consumption in both models. Higher education in both models and being employed in the *trying* model was associated with heavier alcohol consumption.

Perceived infertility as a moderator:

Perceived infertility moderated the relationship between PIS and PA but not between trying and PA (Figure 1). Among participants who perceived infertility risk, the relationship between the PIS and PA was positive, whereas among participants who did not perceive an infertility risk, the relationship between PIS and PA was negative ($p<0.05$) Perceived infertility was not an effect modifier of the relationships between pregnancy intention (PIS or trying) and tobacco smoking or alcohol consumption.

DISCUSSION

For female AYA cancer survivors, navigating fertility and pregnancy post-cancer is complex. With higher infertility and perinatal risks, AYA survivors may benefit from preconception behaviors that benefit fertility and pregnancy. In general populations, pregnancy intention is associated with more PA, less smoking and alcohol use. In our cohort of AYA survivors, urgent pregnancy intention (*trying now)* was associated with more PA, while ambivalent intention was associated with lower alcohol consumption. Taken together, pregnancy intention dimensions were associated with some healthy preconception behaviors and can identify female AYA survivors who may benefit from preconception health education and interventions to change these behaviors.

Compared to the pregnancy intention score (PIS), *trying* was hypothesized to be associated with greater action based on the Rubicon Action model. Indeed, we observed that survivors who reported trying to become pregnant now reported more PA compared to those not trying or with ambivalent intention. Further, aligned with the HBM, perceived susceptibility impacted this relationship: AYA survivors with higher pregnancy intention and believed they were at risk of infertility engaged in more PA compared to women who did not perceive fertility loss. These results are consistent with previous studies in general populations that showed pregnancy intention and PA are significantly associated, and perceived risk (to conceiving or achieving a healthy pregnancy) strengthens this relationship.[27,28] Our findings support that survivors' engagement in PA is influenced by urgent intention.

Measured pregnancy intentions were not associated with smoking and only ambivalent intention was significantly associated with decreased alcohol use. One reason may be that smoking and alcohol consumption are often the last behaviors to change for many women in both intended and unintended pregnancies,[29,30] mostly changing after a pregnancy is recognized and thus not impacting preconception behavior. Interestingly, higher PIS trended towards increased alcohol consumption but this was not significant, while *trying* followed the expected direction of association. This may be an indicator that the PIS score is not sufficient to

capture urgent intention compared to *trying*, especially among behaviors that are shown to be difficult to change or are more likely to change when a pregnancy is realized. Although *trying now* was not significant after model adjustment (most likely due to low power), its direction did indicate it was protective of higher alcohol consumption. A limiting factor was relating pregnancy intention to alcohol intake behavior over the prior year rather than a more narrow time frame. Nonetheless, prevalence of heavy drinking was high in this sample (38.6%) compared to national data on AYA survivors that showed ~14% reported heavy drinking.[31] It is concerning that a large proportion of AYA survivors with increased pregnancy intention were heavy drinkers within a sensitive period of preconception. Providers should screen for problematic alcohol use among AYA survivors, as this may compound neonate risk if an unintended pregnancy is discovered.

A significant proportion of the cohort expressed ambivalent intention, measured as neither trying nor preventing pregnancy. Ambivalent intention represents some level of desire to become pregnant without invoking urgent actions. Interestingly, ambivalent intention was associated with lower alcohol consumption and a non-significant increase in current smoking. Only two prior studies measured ambivalent pregnancy intention in studying preconception behavior. Lundsberg et al., found, among a sample of healthy pregnant women, ambivalence towards a current pregnancy was associated with greater preconception alcohol intake and smoking.[7] In contrast, the 2004 Behavior Risk Factor Surveillance System data showed no association between ambivalent intention and smoking or alcohol intake.[32] While replicative studies can clarify these relationships, we show that ambivalent pregnancy intention is a distinct category with specific health behavior risks. Clinically, providers may consider screening AYA survivors regarding their pregnancy intentions, including ambivalent intention, and tailor preconception health counseling accordingly.

A strength of this study included evaluating pregnancy intention before conception, which is ideal in the context of preconception behaviors. Most studies evaluate intention

retrospectively after pregnancy or birth, which increases recall bias as a woman comes to terms with a pregnancy, both intended or unintended.[33] This study evaluated multiple dimensions of pregnancy intention using measures from the longstanding National Survey for Family Growth and included a measure of ambivalence, however the absence of *attitude* toward pregnancy was a limitation. This dimension asks if participants have a positive, negative or ambivalent attitude when thinking of becoming pregnant.[16] *Attitude* would have made our measure of pregnancy intention more comprehensive by elaborating on the depth of ambivalence towards pregnancy. While distribution of cancer types and psychosocial characteristics of this sample were representative of the larger AYA population, low prevalence of smoking may reflect self-selection of healthy participants who enrolled in a study on ovarian function.[26,34] AYA survivor's knowledge of infertility risks was not directly measured, thus limiting understanding on how knowledge impacts perception of infertility, pregnancy intentions and health behaviors. Other limitations included absence of matched participants with no history of cancer for comparison and limited scope of assessed preconception health behaviors. Additional preconception behaviors like chronic disease management may be particularly important for AYA survivors who often have co-morbidities and would benefit from guidance on behaviors or actions for successful management.

Taken together, the study furthers our understanding of the association between pregnancy intentions and preconception behaviors among female reproductive-age AYA cancer survivors. Results of this study support that screening for pregnancy intention can help providers identify AYA survivors "susceptible" to health behavior change and guide conversations on preconception health. AYA survivors are interested in receiving education and guidance about healthy behaviors however a majority report a lack of communication from providers.[35] Providers caring for AYA survivors may screen for pregnancy intention to guide education and conversations on preconception behaviors even among women reporting ambivalent intention.

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Table 2.1. Demographic and cancer characteristics of female AYA survivors at baseline, 2013-2017

Covariates*	**Baseline** n=1071
Age at questionnaire (mean (SD))	33.3(4.9)
Age at cancer diagnosis (mean (SD))	25.7(5.8)
Race- White	776(74.3)
Black	30(2.9)
Asian/Native Hawaiian/Native Alaskan/Native Indian	76(7.3)
Mixed/Other race	163(15.6)
Hispanic ethnicity	265(25.2)
Heterosexual	992(92.6)
Married/living with partner	737(68.8)
≥ College education	763(71.2)
Employed	815(76.1)
≥$51,000 Household Income	719(67.1)
≥1 Parity	459(42.9)
Health insurance	1025(95.7)
BMI - <18.5	34(3.2)
18.5-24.9	457(42.7)
25-29.9	244(22.8)
≥30	302(28.2)
General Health - Excellent	100(9.3)
Very Good	410(38.3)
Good	429(40.1)
Fair	115(10.7)
Poor	14(1.3)
Cardiovascular/Pulmonary Comorbidities	165 (15.7)
Endocrinological Comorbidities	208 (19.8)
Psychological Comorbidities	292 (27.8)
Other Comorbidities	340 (32.4)
Stress - No/low stress	391(36.5)
Moderate stress	596(55.6)
High stress	84(7.8)
Depression - No significant depression (0-4)	512(47.8)
Mild (5-9)	295(27.5)
Moderate (10-14)	158(15.8)
Severe (15-24)	95(8.9)
Social Support (mean(SD))	4.2(0.9)
Cancer Type - Breast	244(22.8)
Blood/Leukemia/Lymphoma	374(34.9)
Thyroid	120(11.2)
Reproductive (cervix, uterus, ovary)	28(2.6)
Gastrointestinal	74(6.9)
Bone/Soft tissue	32(3.0)
Skin	199(18.6)
Increased Perceived Infertility Risk	678(63.3)
Visited a fertility specialist *(before, during, or after treatment)*	294(28.0)

*Variables depicted as n(%) unless otherwise indicated

Table 2.2. Distribution of pregnancy intention dimensions among female AYA survivors, 2013-2017

Covariates	Total Cohort n=1071 n(%)
Pregnancy Intention Score (corresponding categories of *want* & *planning* dimensions)	
0 (Don't want child/not planning pregnancy)	315(30.7)
0.5 (Don't want child/planning later)	27(2.6)
1 (Want child/not planning pregnancy)	100(9.8)
1.5 (Want child/planning later)	394(38.4)
2 (Want child/planning now)	189(18.4)
Trying	
Not trying	605(56.5)
Neither (Ambivalent)	371(34.6)
Trying now	95(8.9)

Table 2.3. Unadjusted and adjusted models of the association of pregnancy intention score (PIS) with PA (left) and trying to become pregnant with PA (right)

			PIS		Trying	
Covariates	Unadjusted β(95% CI)	p	Adjusted β(95% CI)	p	Adjusted β(95% CI)	p
PIS[§]	0.03(-0.10, 0.24)	0.33	0.05(-0.05, 0.30)	0.18	-	-
Trying to become pregnant-Not trying	Reference		-	-	Reference	
Neither trying nor avoiding	0.04(3.80, 4.11)	0.22	-	-	0.05(-0.09, 0.48)	0.19
Trying now	0.09(0.17, 1.03)	**0.01**	-	-	0.08(0.11, 1.04)	**0.01**
Race-White	Reference		Reference		Reference	
Black	-0.04(-1.18, 0.27)	0.22	-0.03(-1.2, 0.30)	0.24	-0.03(-1.08, 0.41)	0.37
Asian/Native Hawaiian/Native Alaskan/Native Indian	-0.05(-0.83, 0.10)	0.13	-0.06(-1.04, 0.01)	0.05	-0.06(-0.98, 0.03)	0.07
Mixed/Other race	-0.05(-0.62, 0.05)	0.09	-0.06(-0.75, 0.09)	0.13	-0.06(-0.74, 0.10)	0.14
Ethnicity-Non-Hispanic	Reference		Reference		Reference	
Hispanic	-0.04(-0.45, 0.11)	0.24	-0.01(-0.43, 0.30)	0.71	-0.03(-0.48, 0.23)	0.50
Age	0.03(-0.01, 0.04)	0.35	0.07(-0.001, 0.06)	0.06	-	-
Sexual Orientation-Heterosexual	Reference		-	-	Reference	
Homosexual/Other	-0.02(-0.68, 0.32)	0.49	-	-	-0.02(-0.70, 0.36)	0.53
Education-Less than college	Reference		Reference		Reference	
≥College	-0.05(-051, 0.2)	0.08	-0.12(-0.85, -0.21)	**0.001**	-0.12(-0.85, -0.22)	**0.001**
Employment-Unemployed	Reference		-	-	Reference	
Unemployed	0.01(-0.22, 0.35)	0.65	-	-	0.02(-0.24, 0.40)	0.63
Household Income-<$51,000	Reference		Reference		Reference	
≥$51,000	0.02(-0.21, 0.34)	0.64	-0.02(-0.42, 0.22)	0.54	-0.01(-0.35, 0.28)	0.82
Parity-None	Reference		-	-	Reference	
≥1	-0.01(-0.29, 0.20)	0.71	-	-	-0.01(-0.31, 0.24)	0.82
BMI[§]	-0.13(-0.05, -0.02)	**0.001**	-0.11(-0.05, -0.01)	**0.004**	-0.12(-0.05, -0.01)	**0.002**
General Health[§]	-0.19(-0.59, -0.31)	**0.01**	-0.15(-0.54, -0.18)	**0.001**	-0.14(-0.51, -0.15)	**0.001**
Stress-No/low stress	Reference		Reference		Reference	
Moderate	-0.10(-0.66, -0.15)	**0.002**	-0.08(-0.58, -0.02)	**0.03**	-0.07(-0.58, -0.01)	**0.04**
High	-0.08(-1.03, -0.10)	**0.02**	-0.02(-0.71, 0.35)	0.51	-0.03(-0.74, 0.35)	0.49
Social Support	0.08(0.05, 032)	**0.01**	-	-	0.03(-0.09, 0.22)	0.44
Perceived Infertility Risk-No increased risk	Reference		Reference		Reference	
Increased risk	0.05(-0.03, 0.47)	0.08	0.07(0.02, 0.57)	**0.03**	0.06(-0.01, 0.55)	0.06

[§]Variables kept continuous in analysis

Table 2.4. Unadjusted and adjusted models of the association of pregnancy intention score (PIS) with smoking (left) and trying to become pregnant with smoking (right)

Covariates	Unadjusted OR(95% CI)	p	PIS Adjusted OR(95% CI)	p	Trying Adjusted OR(95% CI)	p
PIS[§]	0.68(0.50-0.94)	**0.02**	0.73(0.50-1.07)	0.11	-	-
Trying to become pregnant-Not trying	Reference		-	-	Reference	
Neither trying nor avoiding	2.12(1.26-3.55)	**0.005**	-	-	1.72(0.94-3.14)	0.08
Trying now	0.46(0.11-1.96)	0.29	-	-	0.76(0.19-3)	0.69
Race-White	Reference		Reference		Reference	
Black	1.15(0.27-4.98)	0.85	0.59(0.14-2.48)	0.47	0.51(0.12-2.06)	0.34
Asian/Native Hawaiian/Native Alaskan/Native Indian	0.91(0.32-2.6)	0.86	1.81(0.62-5.3)	0.28	1.33(0.46-3.86)	0.60
Mixed/Other race	0.95(0.46-1.99)	0.90	0.79(0.31-2.04)	0.63	0.82(0.32-2.11)	0.68
Ethnicity-Non-Hispanic	Reference		Reference		Reference	
Hispanic	1.13(0.64, 2.01)	0.67	0.58(0.25, 1.31)	0.19	0.51(0.22, 1.17)	0.11
Education-Less than college	Reference		-	-	Reference	
≥College	0.35(0.21-0.58)	**0.00**	-	-	0.61(0.33-1.14)	0.12
Household Income-<$51,000	Reference		Reference		Reference	
≥$51,000	0.33(0.19-0.56)	**0.00**	0.30(0.16-0.55)	**0.00**	0.37(0.20-0.70)	**0.002**
Parity-None	Reference		Reference		Reference	
≥1	1.90(1.14-3.17)	**0.01**	2.18(1.17-4.05)	**0.01**	2.05(1.11-3.78)	**0.02**
Health insurance-No	Reference		Reference		Reference	
Yes	0.32(0.14-0.75)	**0.01**	0.27(0.1, 0.7)	**0.01**	0.33(0.13, 0.84)	**0.02**
Social Support(mean(SD))	0.57(0.45-0.72)	**0.001**	0.61(0.47, 0.80)	**0.001**	0.63(0.48, 0.82)	**0.001**
Perceived Infertility Risk- No increased risk	Reference		Reference		Reference	
Increased risk	1.04(0.62, 1.76)	0.88	1.12(0.61, 2.07)	0.72	1.00(0.53, 1.87)	0.99

[§]Variables kept continuous in analysis

Table 2.5. Unadjusted and adjusted models of the association of pregnancy intention score (PIS) with alcohol consumption (left) and trying to become pregnant with alcohol consumption (right)

Covariates	Unadjusted OR(95% CI)	p	PIS		Trying	
			Adjusted OR(95% CI)	p	Adjusted OR(95% CI)	p
PIS[§]	1.20(1.03-1.40)	**0.02**	1.12(0.95-1.33)	0.18	-	-
Trying to become pregnant-Not trying	Reference		-	-	Reference	
Neither trying nor avoiding	0.65(0.51-0.84)	**0.001**	-	-	0.72(0.55-0.95)	**0.02**
Trying now	0.82(0.55-1.24)	0.36	-	-	0.79(0.5-1.22)	0.28
Race-White	Reference		Reference		Reference	
Black	0.70(0.34, 1.44)	0.33	0.75(0.35-1.59)	0.45	0.70(0.34-1.46)	0.35
Asian/Native Hawaiian/Native Alaskan/Native Indian	0.49(0.31, 0.77)	**0.002**	0.37(0.22-0.61)	**0.001**	0.47(0.29-0.76)	**0.002**
Mixed/Other race	0.67(0.48, 0.92)	**0.01**	0.91(0.62-1.34)	0.63	0.95(0.64-1.39)	0.78
Ethnicity-Non-Hispanic	Reference		Reference		Reference	
Hispanic	0.58(0.44, 0.76)	**0.001**	0.77(0.55, 1.09)	0.14	0.75(0.54, 1.05)	0.09
Education-Less college	Reference		Reference		Reference	
≥College	2.12(1.64-2.76)	**0.001**	1.72(1.28-2.31)	**0.001**	1.52(1.13-2.05)	**0.01**
Employment-Unemployed	Reference		-	-	Reference	
Employed	1.98(1.49-2.62)	**0.001**	-	-	1.62(1.21-2.19)	**0.001**
Parity-None	Reference		Reference		Reference	
≥1	0.61(0.48-0.78)	**0.001**	0.62(0.47, 0.81)	**0.001**	0.62(0.48-1.18)	**0.001**
General Health-Excellent	0.68(0.59-0.78)	**0.001**	0.70(0.60-0.82)	**0.001**	Reference	
Very Good	-	-	-	-	0.75(0.48-1.18)	0.21
Good	-	-	-	-	0.53(0.34-0.84)	**0.01**
Fair	-	-	-	-	0.46(0.26-0.8)	**0.01**
Poor	-	-	-	-	0.30(0.1-0.92)	**0.03**
Perceived Infertility Risk-No increased risk	Reference		Reference		Reference	
Increased risk	1.12(0.88, 1.42)	0.36	1.16(0.89, 1.51)	0.29	1.18(0.90, 1.55)	0.22

[§]Variables kept continuous in analysis

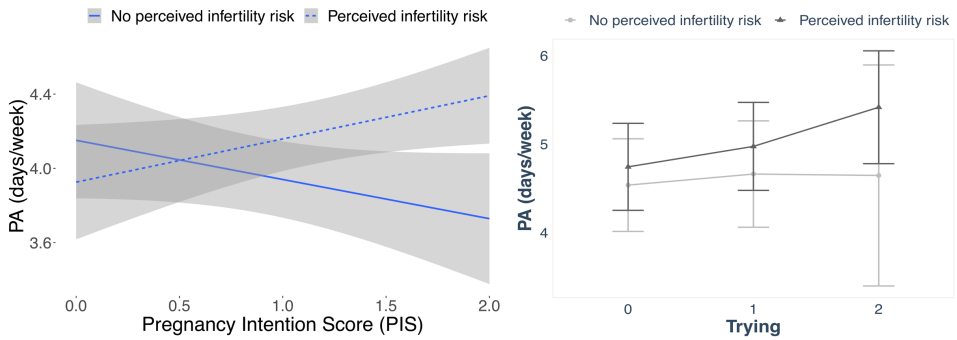

Figure 2.1. Effect modification by perceived infertility risk: Predicted physical activity (PA) and 95% CI by pregnancy intention score, stratified by perceived infertility risk (left); mean PA (SD) by trying dimension, stratified by perceived infertility risk (high).

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CHAPTER 3

The effect of changing pregnancy intentions on preconception health behaviors: a prospective cohort study

ABSTRACT

Purpose: Pregnancy intentions are associated with preconception health behaviors but are understudied among female adolescent and young adult (AYA) cancer survivors. Preconception health is critical for survivors because they face unique risks to fertility and pregnancy from late effects of cancer treatments. This study prospectively assessed the effect of pregnancy intention on physical activity (PA) and smoking behaviors among female AYA survivors.

Methods: A cohort of 1049 female AYA survivors were recruited between 2013-2017. Participants were 18-39 years and had completed primary cancer treatment. Longitudinal mixed effects analysis was conducted on participants who completed at least 2 of 4 questionnaires over 1.5 years. Two measures were used to capture multiple dimensions of pregnancy intention. The pregnancy intention score (PIS) captured *wanting* and *planning* dimensions and represented a scaled response of low to high intention. The *trying* dimension captured urgent intention and ranged from not trying, ambivalent (neither attempting nor avoiding pregnancy), and trying now. Intention change was assessed between each consecutive time points. Final analysis was conducted with multiple imputations.

Results: Survivors with increased intention measured by *trying* was associated with increased PA over time (adjusted B [95%CI]: 0.3 [0.01, 0.5]) compared to survivors with no changes or decreased *trying* intention. PIS was not significantly associated with preconception behaviors. No measure of intention was associated with smoking behavior.

Conclusions: Increasingly urgent pregnancy intention (*trying* dimension) was associated with higher preconception PA.

Implications for Cancer Survivors: Screening for immediate intentions can identify AYA survivors in need of early preconception health promotion.

INTRODUCTION

Fertility and family planning are key areas of focus for adolescent and young adult cancer (AYA) survivors [1]. Preconception health is critical for survivors because they face unique risks to fertility and pregnancy health due to late effects of cancer treatments, are susceptible to unplanned pregnancies, and are known to engage in unhealthy behaviors (i.e., smoking, binge drinking) [2–4]. Two key modifiable health behaviors during preconception include physical activity (PA) and cigarette smoking [5]. Both have significant effects on maternal and neonatal health, while smoking can also reduce fertility among women [6–8]. Strategies to reduce adverse health behaviors prior to conception in AYA survivors can improve pregnancy health and outcomes.

Pregnancy intentions are associated with health behaviors however these findings are not consistent and methodologically limited [9–11]. Pregnancy intention is a multifaceted concept that represents a spectrum of intended actions to achieve or avoid a pregnancy [12,13]. Different dimensions of intention like *wanting* a child, *planning* to become pregnant, and *trying* represent levels of urgency to become pregnant and are theorized to be associated with behavior as urgency increases [14]. Additionally, intentions are known to change before and throughout pregnancy as life circumstances change for women [12]. Currently, most studies assess pregnancy intention at one time point, retrospectively, and mainly by the *planning* dimension [11,15]. In a systematic review of the association between pregnancy intention and health behaviors, Hill et al., 2019 found among 303 studies only 7% evaluated intention prospectively, and most evaluated general levels of pregnancy intention at one time point [11]. Each of these methods can lead to bias in findings. In particular, retrospective assessment of intention can lead to biased results in which, for example, unintended pregnancies are underestimated because wantedness as an intention increases during a pregnancy [15,16].

Prospective assessment of pregnancy intention with repeated evaluation is needed to better understand the role of pregnancy intention on preconception health behavior.

Collectively there is limited understanding of how pregnancy intentions may impact female AYA survivors' preconception behavior, especially longitudinally. Intentions to become pregnant is high among cancer survivors, upwards of 60-78%, and often is high regardless of the type of cancer and treatments experienced [17,18]. Despite this, most studies with cancer survivors focus on factors associated with unplanned pregnancies or attempt to contextualize why survivors may or may not desire to have children after cancer [19–21]. Only one study evaluated the association between pregnancy intentions and preconception behaviors among female AYA survivors and found intentions during preconception were positively association with PA, but only cross-sectionally [14]. The current study furthers our knowledge by understanding longitudinal associations of changing pregnancy intention on preconception PA and smoking. It is hypothesized that increased pregnancy intentions will be associated with higher engagement in healthy preconception behaviors among AYA cancer survivors.

METHODS

This study used data from the Reproductive Window in Young Adult Cancer Survivors (WINDOW) study, a prospective cohort study to estimate the trajectory of ovarian function among AYA survivors [22]. The State of California Committee for the Protection of Human Subjects and the Institutional Review Boards at the University of California, San Diego, and the Texas Department of State Health Services approved the WINDOW study. Participants were recruited through California and Texas cancer registries, social media, and physician referrals. Eligible participants included females, 18-39 years old, diagnosed with cancer between 15-39 years of age, at variable intervals since completing primary cancer treatment, and had at least one ovary. Exclusion criteria were uncontrolled endocrinopathies and multiple cancers or

recurrence. Participants were followed for 18 months between 2013-2017 and were asked to complete study questionnaires that included assessment of pregnancy intentions and preconception behaviors every 6 months. If participants missed replying to a survey at any follow-up they were still included and asked to complete surveys at the next study follow-up. For this analysis, participants who completed at least 2 surveys were included. Women who were pregnant or breastfeeding at each time point were excluded.

Measurements:

Pregnancy intention. Multiple dimensions of pregnancy intention were assessed by two variables: the Pregnancy Intention Score (PIS) and attempting pregnancy now (*trying* dimension). These specific measures of intention were utilized because they correlate with urgent vs. non-urgent intention based on the Rubicon Action Model [14,23]. Specifically PIS is associated with non-urgent intention and the *trying* dimension represents urgent intention. Per the Rubicon Action Model urgency of intention translates to higher likelihood of action [14,23]. The PIS represents a summed score of *wanting* and *planning* dimensions of pregnancy intention on a 5-point scale ranging from low intention (PIS=0) (not wanting/planning of a child to wanting) to high intention (PIS=2) (planning a pregnancy now) [14]. When evaluated for internal consistency, the scale showed good reliability (Cronbach α= 0.8).

One item captured the dimension of *trying* where participants reported if they were attempting to become pregnant now. Responses included *yes-trying now*, *no-avoiding pregnancy,* and *neither trying nor avoiding pregnancy*. *Neither* responses were categorized as ambivalent intention as an umbrella term for any reasons for indecision towards pregnancy. Further details on the creation of the PIS and the use of both measures is discussed separately [14].

Change in pregnancy intention. Changes in pregnancy intention were captured at each 6-month increment compared to the last time point. Categories included: no change in intention,

increased intention, and decreased intention. Numeric changes between 0.5-2 in the PIS reflected change in intention. For the *trying* dimension, *not trying* represented lowest pregnancy intention, whereas *trying now* represented highest intention with ambivalent responses in the middle. Any change between these responses, respectively, reflected increasing or decreasing intention. For example, change from *not trying* to ambivalent represented an increase in intention.

Physical activity. Participants were asked how many days they were physically active in the past 7 days for at least 30 minutes/day, including PA that increased heart rate and breathing. This one-item tool from NHANES Physical Activity Questionnaire has test-retest reliability (r=0.72- 0.82) in adult and adolescent populations and had modest concurrent validity with objective measures of activity when compared to more comprehensive scales like the Global Physical Activity Questionnaire and Oxford Physical Activity Questionnaire [24–26].

Current smoking behavior. Participants were asked if they currently smoke tobacco with final responses as: *current smoker* (includes *daily* and *less than daily*) and *non-smoker* [27]. *Don't know* responses were excluded from analysis.

Perceived infertility risk. Participants were asked if they felt their own fertility was greater, same, or less than their female peers [28]. Responses were collapsed to compare any perception of increased risk to no perception of increased risk. Final categories were: *no increased risk* (includes greater or same level of fertility) and *increased risk* (includes less fertile or infertile).

Confounders. Demographic covariates included age, race, ethnicity, sexual orientation, education, income, marital status, and health insurance coverage. Respondents ranked their overall general health with 5 responses from excellent to poor. Body mass index (BMI) was calculated with self-reported weight and height. Self-reported comorbidities were categorized as cardiovascular/pulmonary, endocrine, psychological, and other comorbidities. Additional covariates identified as potential confounders included parity and consultation with a fertility

specialist before, during or after cancer treatment. Psychosocial factors included stress measured by the Perceived Stress Scale-10 [29], depression measured by the Patient Health Questionnaire depression scale [30], and social support by RAND institutes medical outcomes study survey [31]. Time since cancer treatment was assessed as a potential confounder.

Statistical analysis:

The exposure was change in pregnancy intention in both PIS and *trying* to become pregnant. Outcomes were days of PA in the last week and current smoking behavior. Covariates were assessed for multicollinearity and reduced if closely associated (Rho >=0.5). Remaining covariates were assessed for time variation and if significantly changing overtime, were included as time-varying covariates. All covariates were included and then reduced if non-significant in models and did not present confounding (≤ 10% change in parameter). Frequencies of each variable were described and bivariate tests of association were determined with generalized mixed effects models.

Multivariable mixed effects models, to allow for individual outcome trajectories, were used to model preconception behavior changes. Time was kept categorical within analyses to compare changes over time from baseline. Change in intention was lagged to evaluate outcomes at each consecutive 6-month time point. Thus the first change variable assessed intention change from baseline to 6 months and this was evaluated with behavioral outcomes at the 6-month survey time point. Linear mixed effect models (LMMs) evaluated changes in days of PA and Generalized LMMs (GLMMs) modeled changes in smoking status over each survey time point. The 'lme4' package in R Studio Version 1.2.5001 was used to analyze both the LMM and GLMMs models [32]. Perceived infertility risk and parity were assessed as effect modifiers in each final parsimonious model as both interaction terms and by stratified analysis.

The main analysis was conducted with multiple imputation (MI) to mitigate reduced power and bias due to attrition [33]. MI estimated missing values using models developed with

data from complete cases (participants with no missing data). Missing values were retained at the baseline time point for change in intention variables. MI was conducted in R with the Multiple Imputation Chain Equation (MICE) package and final models were pooled over 60 imputed data sets and summarized [34]. Further information on the specifications used for MI in this study is included in Supplementary File 1. Demographic differences were assessed between responders and nonresponders with each behavior model.

RESULTS

More than 30,000 recruitment letters were sent to potentially eligible individuals identified by the California and Texas cancer registries, social media, and physician referrals. Of this group n=1825 contacted the study team and were assessed for eligibility, 1269 were eligible, and 1159 consented to the study. A total of 1071 eligible participants completed baseline surveys, of which 22 were excluded at baseline because they were either pregnant or breastfeeding. Overall, 65% of the cohort responded to at least 2 surveys and were included in final analyses (Figure 1). Mean age at cancer diagnosis was 25.7 (standard deviation (SD): 5.8) and mean time to interview from cancer diagnosis was 7.6 (SD: 4.9) years. Baseline characteristics of the cohort are reported in Table 1. At enrollment, most participants were White (74.3%), non-Hispanic (74.8%), partnered (68.8%), and had a mean age of 33 years. Common cancers survived were blood/leukemia/lymphoma (34.9%), breast (22.8%), and skin (18.6), and most participants considered themselves to be at risk of infertility (63.3%). Employment status, household income, and parity were included in models as time-varying covariates.

Longitudinal variation in pregnancy intention was observed both within individuals (data not shown) and over time for the overall cohort (Figure 2). Only 25% and 17% of participants reported the same level of PIS and *trying* intention at each follow-up time point, respectively. Mean PIS and proportion of *trying* to become pregnant significantly reduced over time in

Asian/Native Hawaiian/Alaskan/Indian groups and differed by BMI, stress, and perceived infertility risk (Supplementary File 2). Only PIS increased among parous participants.

Physical Activity

Over time, participants reported significantly less PA (Supplementary File 2). Pooled estimates from MI models reflected increased *trying* intention was associated with increased PA over time (adjusted B [95%CI]: 0.3 [0.01, 0.5]) compared to participants with no changes in intention (Table 2). Participants with decreased intention did not differ significantly in PA from participants with no change in intention (adjusted B [95%CI]: 0.2 [-0.1, 0.5]). Adjusted analysis with complete cases saw similar significant association with increased *trying* dimension associated with increased PA (B 0.2 [0.04, 0.32]) (Table 2). Changes in PIS intention in both MI and complete case models was not associated with PA over assessments (Table 2). Post hoc analysis describing missing data patterns compared participant demographics with PA responses vs. those missing any PA data showed a higher proportion of missing participants were Hispanic, had less than a college education, and, at later time points, were less likely to be White and more likely to be mixed/other race ($p < 0.005$). Race, ethnicity, and education were retained in all final evaluative models along with other covariates for adjustment.

Current smoking behavior

The proportion of current smokers reduced among participants over time (Supplementary File 2). In both pooled estimates from MI models and complete case models no significant differences were found between those with changing intentions (decreased or increased) compared to participants with no change in intention (Table 2). Post hoc analysis of predictors of missingness showed a higher proportion of cases with missing smoking status reported ambivalent intention and attempting pregnancy now, were Hispanic, and of a lower

household income (p<0.005). Ethnicity, and income were retained in all final evaluative models along with other covariates for adjustment.

In each model of PA and smoking, evaluation of two-way interaction terms between perceived infertility risk and PIS or *trying* intentions did not support effect modification in either pooled MI models or complete case analyses. When stratified by perceived infertility risk, decreased *trying* intention was associated with higher odds (2.5 [1.2, 5.7]) of smoking among participants who perceived fertility risk, while PIS was not associated with PA or smoking in either stratum in pooled MI models (Supplementary File 2 Table 5). Two-way interaction terms between parity and PIS or *trying* did not show effect modification in either pooled MI models or complete case analysis. When stratified by parity, effect modification was seen as increased PIS (adjusted B 0.6 [95%CI: (0.1, 1.1)]) and trying intention (adjusted B 0.3 [95% CI 0.03, 0.5]) was associated with PA in parous but not nulliparous participants (Supplementary File 2 Table 6).

DISCUSSION

Preconception is a significant period for reproductive-aged women, especially for AYA survivors who may experience greater infertility and perinatal risks [35]. Healthy behaviors during this period can increase the likelihood of a healthy pregnancy and positive neonatal outcomes. Previous studies found positive associations between pregnancy intention and health behaviors among general populations of reproductive aged women, but few explored relationships in AYA survivors and many were methodologically limited [9,11]. This longitudinal study found that women who began to attempt pregnancy reported higher PA, compared to women with no change in intention. Pregnancy intentions measured by the PIS, or non-urgent intention, were not associated with behavior changes and no measure of intention was associated with smoking behavior. Taken together, urgent intention to become pregnant

influences engagement in preconception PA and can be utilized to screen and identify survivors receptive to preconception support and intervention.

Increasing intention measured by *trying* to become pregnant was associated with preconception PA. Although some studies have found higher PA among intended pregnancies [36,37], one study found that after controlling for maternal variables like BMI and education, differences in PA by *planning* intention, were no longer significant [38]. Here the measurement of intention may explain conflicting findings. *Trying* represents an urgent intention and was hypothesized to be more likely to impact behavior based on behavioral theories [14,23]. The dimensions of pregnancy intention captured within PIS (*wanting* and *planning)* are generally considered attitudinal intentions, not behavioral intentions [12]. Attitudinal intentions are informational and play a role in intention development however, our study indicates when considering behavior change, measures of urgent intention are more robust. *Trying* as a dimension is not commonly used in intention studies, in contrast to *planning* or *want* intentions. Both the *London Measure of Unplanned Pregnancy (LMUP),* considered a gold standard of pregnancy intention measures, and the *One Key Question (OKO)*, a validated measure widely used in clinical settings, evaluate intention primarily from the *planning* and *want* perspectives, respectively [41,42]. Stratified analysis suggested that PIS and trying were associated with PA among parous survivors (but not among nulliparous survivors); findings require future replication as nulliparous women are more likely to report more preconception PA compared to parous women in general populations [39,40]. In the context of behavior change in the AYA cancer survivor population, our findings highlight the utility of urgent measures of intention like *trying*.

This study did not find any association between changing pregnancy intentions and current smoking behaviors. Stratified analysis suggested that participants with perceived infertility risk may be more likely to smoke when they do not intend to try to become pregnant, but results need replication because the sample size of those who did not perceive infertility risk was small. Selection bias may have limited these findings as only 6% (n=64) of the baseline

cohort reported smoking when other studies have reported higher proportions of female AYA survivors smoke (27-29%) [2,43]. However, smoking in general is a difficult behavior to modify and most women do not cease smoking till a pregnancy is recognized [44,45]. Most studies in general populations of women have found no association between intention and smoking behavior, only one study found ambivalent intention was associated with increased smoking behavior [46]. Because pregnancy intention was not associated with smoking behavior, screening for pregnancy intention would likely not tailor smoking cessation discussions for AYA survivors. Different avenues of intervention are needed because AYA survivors do experience unexpected pregnancies and may be exposed to harmful effects of smoking during a sensitive period.

This study made use of MI to retain power in analysis. This study saw an overall 58% loss to follow-up, which is common for prospective cohort studies [47]. Compared to responders, nonresponse was found to be highest among those of Hispanic ethnicity, non-white race, lower income and lower education. Nonresponse is known to be higher among individuals in these demographics [48–50]. In our study we hypothesized data was *missing at random* (MAR) which assumes missing data or nonresponse is associated only with observed data and not with unobserved data [47]. MAR gives validity to MI because variables predictive of missingness (i.e., Hispanic ethnicity, non-white race) are included in MI estimations and allows for greater accuracy in estimation [51]. Because demographic variables were identified that could estimate likelihood of nonresponse, MAR was a valid assumption for our study and supported robust MI estimations. Additionally results did not differ between complete case and MI models indicating MI provided greater accuracy in our estimations without adding bias.

A key strength of this study is the prospective evaluation of changing pregnancy intentions every 6 months during the preconception period among AYA survivors. Fluctuation is a characteristic of pregnancy intention because it follows a constructivist formation; situation, environment, time, among many other variables, influence and contribute to the formation of

intention [52]. As these external variables change so may intention. Martial status/having a partner, employment, and household income are shown to contribute to changes in pregnancy intentions [53]. During preconception, we saw an overall decrease in intentions whereas previous studies primarily assessed intention change from preconception to post-partum, and here intention increases over time [16,54]. Given the mean age of our cohort, increasing age may be a reason for a downward trend in intention. Older women, especially women 35+, are more likely to report lower reproductive intentions among general populations and cancer survivors [55,56]. This aligns with the constructivist model as pregnancy intention is constantly being reassessed as life circumstances change.

A limitation in our study included the lack of assessment of AYA survivor knowledge on preconception health and healthy behaviors. Knowledge may impact preconception behaviors and would have identified gaps and areas of intervention. Additionally, this study only assessed 2 modifiable behaviors whereas additional preconception behaviors like managing chronic health conditions may be particularly important for AYA survivors who often have co-morbidities and would benefit from guidance on successful management.

CONCLUSION

This study furthers our understanding of changing pregnancy intentions and the role of these changes on preconception behaviors among female reproductive-age AYA cancer survivors. Urgent dimensions of pregnancy intention are associated with PA behavior and repeated assessments of intention strengthen findings by capturing changes in pregnancy intention during preconception. Early preconception education and intervention can help women navigate family planning and achieve healthy pregnancies. National guidelines highlight the role of health care providers in guiding family planning, providing education and health promotion during clinic visits [6]. Incorporation of urgent pregnancy intention screening in survivorship care can help facilitate early preconception health promotion and education.

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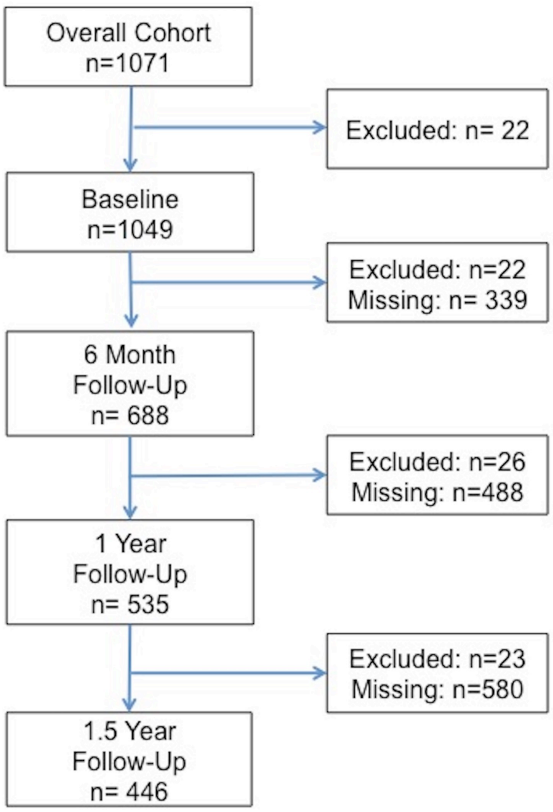

Figure 3.1. Number of participants at each study time point, who were included in the study cohort, were missing, or were excluded due to an existing pregnancy or reported breastfeeding.

Table 3.1. Demographic and cancer characteristics of female AYA survivors (n=1049), 2013-2017

Covariates*	
Age at questionnaire (mean (SD))	33.3 (4.9)
Race	
White	776 (74.3)
Black	30 (2.9)
Asian/Native Hawaiian/Native Alaskan/Native Indian	76 (7.3)
Mixed/Other race	163 (15.6)
Hispanic ethnicity	265 (25.2)
Heterosexual	992 (92.6)
Married/living with partner	737 (68.8)
≥ College education	763 (71.2)
Employed	815 (76.1)
≥$51,000 Household Income	719 (67.1)
≥1 Parity	459 (42.9)
Health insurance	1025 (95.7)
BMI	
<18.5	34 (3.2)
18.5-24.9	457 (42.7)
25-29.9	244 (22.8)
≥30	302 (28.2)
General Health	
Excellent	100 (9.3)
Very Good	410 (38.3)
Good	429 (40.1)
Fair	115 (10.7)
Poor	14 (1.3)
≥1 Comorbidities	810 (75.6)
Stress	
No/low stress	391 (36.5)
Moderate stress	596 (55.6)
High stress	84 (7.8)
Depression	
No significant depression (0-4)	512 (47.8)
Mild (5-9)	295 (27.5)
Moderate (10-14)	158 (15.8)
Severe (15-24)	95 (8.9)
Social Support (mean(SD))	4.2 (0.9)
Cancer Type	
Breast	244 (22.8)
Blood/Leukemia/Lymphoma	374 (34.9)
Thyroid	120 (11.2)
Reproductive (cervix, uterus, ovary)	28 (2.6)
Gastrointestinal	74 (6.9)
Bone/Soft tissue	32 (3.0)
Skin	199 (18.6)
Ever visited fertility specialist	294 (27.5)
Increased Perceived Infertility Risk	678 (63.3)

*Variables depicted as n(%) unless otherwise indicated

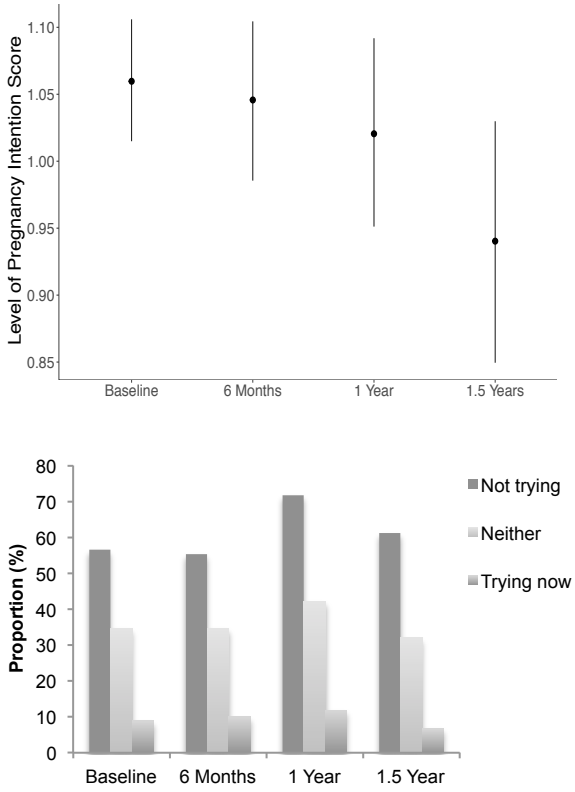

Figure 3.2. Sample mean and 95% CI of the pregnancy intention score (above) and proportions of the *trying* pregnancy intention (below) over time

Table 3.2 Mixed effects models of the association of changes in pregnancy intention score (PIS) (left) and trying to become pregnant (right) with physical activity and smoking

	Physical Activity				Smoking			
	PIS[a]		Trying[b]		PIS[c]		Trying[d]	
	Adjusted B (95% CI)	p	Adjusted B (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
Multiple Imputation Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	References		References	
Decreased Intention	0.6 (-0.2, 0.3)	0.6	0.2 (-0.1, 0.5)	0.1	1.5 (0.62, 3.56)	0.4	1.67 (0.78, 3.53)	0.2
Increased Intention	0.2 (-0.1, 0.4)	0.2	0.3 (0.01, 0.5) 0.	0.04	1.35 (0.69, 3.56)	0.5	1.06 (0.41, 2.80)	0.9
Random Effects	1.7		1.7		7.8		5.4	0.06
Complete Cases Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	References		References	
Decreased Intention	0.001 (-0.1, 0.1)	0.9	0.1 (-0.05, 0.23)	0.2	2.5 (0.66, 9.31)	0.2	3.3 (0.8, 13.5)	0.1
Increased Intention	0.14 (-0.1, 0.29)	0.05	0.2 (0.04, 0.32)	0.01	1.1 (0.20, 5.78)	0.9	0.5 (0.1, 4.5)	0.5
Random Effects	1.6		1.7		3.3		3.3	

[a] Model adjusted for time, race, ethnicity, age at baseline, education, BMI, general health, stress, social support, perceived infertility risk
[b] Model adjusted for time, race, ethnicity, age at baseline, education, employment, household income, BMI, general health, stress, perceived infertility risk
[c] Model adjusted for time, age at enrollment, race, ethnicity, education, marital status, employment, income, BMI, general health, presence of insurance, stress, social support, comorbidities, parity, perceived infertility risk
[d] Model adjusted for time, race, ethnicity, employment, income, perceived infertility risk

SUPPLEMENTAL INFORMATION I

Methods on Multiple Imputations:

Multiple imputations was conducted through the R package Multiple Imputation Chain Equation (MICE) package. MICE was ran with fully conditional specification (FCS) modeling which runs iterative regressions of a variable's values to estimate a distribution of the observed values.[1] This distribution is then utilized to estimate missing values. Each model was ran with 60 iterations based on the largest value of missingness within the dataset. A missing at random assumption was made for the analysis because difference between responders and nonresponders were captured by observed characteristics and there were no theoretical underlying reasons for missingness based on nonobserved data.[2] To improve estimation of missing values covariates that may predict missingness and were to be included in final analyses were included in MI models.[2] By including these covariates relationships between variables are preserved which help in estimation.

Within MICE coding, classification and regression trees (CART) method was used because it works well with continuous and categorical data, preserves the value range in which missing data can be estimated, and does not rely on parametric assumptions for imputation.[3] This was important so that predicted values of categorical variables remain within appropriate categories.

Table S3.1. Proportions of missingness and complete cases across independent and outcome variables

	Cases with Missing Data			Complete Cases
	6 Months n(%)	**1 Year** n(%)	**1.5 Years** n(%)	**n(%)**
Independent Variables				
PIS	409 (38.4)	553 (51.9)	663 (62.3)	338 (31.7)
Trying	377 (35.4)	530 (49.8)	642 (60.2)	389 (36.5)
Outcomes				
PA	377 (35.4)	530 (49.8)	642 (60.2)	389 (36.5)
Smoking	381 (35.8)	535 (50.2)	643 (60.4)	382 (35.9)

References:

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2. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ*. 2009;339(7713):157-160. doi:10.1136/bmj.b2393

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SUPPLEMENTAL INFORMATION II

Table S3.2. Mean Pregnancy Intention Score (PIS) (standard deviation) over time by participant characteristics

Covariates	Baseline n= 1049 Mean (SD)	6 Months n= 688 Mean (SD)	1 Year n= 535 Mean (SD)	1.5 Years n= 446 Mean (SD)
Overall Cohort	3.1 (1.5)	3.1 (1.6)	3.0 (1.6)	2.9 (1.6)
Race- White	3.1 (1.5)[a]	3.0 (1.6)	3.0 (1.6)	2.8 (1.6)
Black	3.6 (1.4)	3.6 (1.4)	4.1 (0.7)	3.8 (1.2)
Asian/Native Hawaiian/Alaskan/Indian*	3.6 (1.4)	3.7 (1.2)	3.4 (1.4)	3.0 (1.6)
Mixed/Other race	3.0 (1.6)	3.1 (1.6)	3.1 (1.6)	2.9 (1.7)
Hispanic ethnicity- Non-Hispanic	3.1 (1.5)	3.1 (1.6)	3.0 (1.6)	2.9 (1.6)
Hispanic	3.1 (1.5)	3.1 (1.5)	2.9 (1.6)	2.8 (1.6)
Education*- High school or less	3.0 (1.5)	2.8 (1.6)[a]	2.7 (1.5)[a]	2.6 (1.6)
≥ College education	3.2 (1.5)	3.2 (1.6)	3.1 (1.6)	2.9 (1.6)
Marital Status- Not married/ partnered	3.2 (1.3)	3.1 (1.3)	3.2 (1.3)	3.1 (1.5)
Married/ partnered	3.1 (1.6)	3.1 (1.7)	2.9 (1.7)	2.8 (1.7)
Employment- Unemployed	3.0 (1.5)	3.0 (1.6)	3.1 (1.6)	2.8 (1.6)
Employed	3.2 (1.5)	3.1 (1.6)	3.0 (1.6)	2.9 (1.6)
Household Income < $51,000	3.3 (1.4)	3.2 (1.4)	3.1 (1.4)	3.1 (1.5)
≥ $51,000	3.1 (1.6)	3.1 (1.6)	3.0 (1.7)	2.8 (1.7)
BMI*- <18.5	3.2 (1.4)	3.0 (1.7)	2.9 (1.7)[a]	2.8 (1.8)
18.5-24.9	3.2 (1.5)	3.2 (1.5)	3.2 (1.5)	2.9 (1.6)
25-29.9	3.1 (1.6)	3.2 (1.7)	3.1 (1.7)	2.9 (1.7)
≥30	3.0 (1.6)	2.9 (1.6)	2.7 (1.6)	2.8 (1.6)
General Health- Excellent	3.1 (1.7)	2.9 (1.6)	3.0 (1.6)	2.9 (1.7)
Very Good	3.1 (1.6)	3.2 (1.6)	3.1 (1.6)	2.9 (1.7)
Good	3.1 (1.5)	3.1 (1.5)	3.1 (1.5)	2.9 (1.5)
Fair	3.1 (1.6)	3.1 (1.6)	2.9 (1.6)	2.5 (1.8)
Poor	3.0 (1.5)	2.5 (1.6)	2.5 (1.6)	2.5 (2.1)
Health Insurance- No insurance	3.3 (1.5)	3.2 (1.5)	3.3 (1.6)	3.0 (1.8)
Has insurance	3.1 (1.5)	3.1 (1.6)	3.0 (1.6)	2.9 (1.6)
Stress* - No/low stress	3.0 (1.6)	3.1 (1.6)	3.0 (1.6)	2.9 (1.6)
Moderate stress	3.2 (1.5)	3.1 (1.6)	3.1 (1.5)	2.9 (1.6)
High stress	3.1 (1.4)	2.9 (1.7)	3.0 (1.6)	2.6 (1.6)
Presence of cardiopulmonary comorbidities- No	3.1 (1.5)	3.1 (1.6)	3.0 (1.6)	2.9 (1.6)
Yes	3.1 (1.5)	3.3 (1.5)	3.2 (1.5)	3.0 (1.6)
Presence of psychological comorbidities- No	3.2 (1.5)	3.1 (1.6)	3.0 (1.6)	2.8 (1.6)
Yes	3.0 (1.5)	2.9 (1.6)	3.0 (1.5)	3.0 (1.6)
Presence of endocrine comorbidities- No	3.2 (1.5)	3.1 (1.6)	3.1 (1.6)	2.9 (1.6)
Yes	3.0 (1.6)	3.1 (1.6)	2.9 (1.6)	2.8 (1.6)
Presence of other comorbidities- No	3.1 (1.6)	3.2 (1.6)	3.1 (1.6)	3.1 (1.6)[a]
Yes	3.1 (1.5)	3.0 (1.6)	2.9 (1.6)	2.6 (1.6)
Parity*- None	3.5 (1.3)[a]	3.1 (1.6)[a]	3.0 (1.6)	2.9 (1.6)
≥1 Parity	2.6 (1.6)	4.8 (0.5)	3.3 (2.0)	3.2 (1.5)
Perceived Infertility Risk*- No increased risk	2.8 (1.6)[a]	2.7 (1.6)[a]	2.8 (1.6)[a]	2.4 (1.6)[a]
Increased risk	3.3 (1.5)	3.3 (1.5)	3.2 (1.5)	3.2 (1.6)

*Significant difference in mean PIS across time points ($p < 0.05$)
[a]Significant difference in mean PIS between covariate groups at applicable time point ($p < 0.05$)

Table S3.3. Distribution of attempting pregnancy (*trying* dimension) over time by participant characteristics

Covariates[§]	Baseline			6 Month			1 Years			1.5 Years		
	Not Trying n= 590	Ambivalent n= 364	Trying Now n= 95	Not Trying n=385	Ambivalent n=235	Trying Now n=68	Not Trying n=308	Ambivalent n=177	Trying Now n=50	Not Trying n=261	Ambivalent n=135	Trying Now n=27
Age at questionnaire* (mean (SD))	32.8(5.0)	33.8(4.9)	34.3(4.1)[a]	32.8(5.0)	33.7(4.7)	34(3.5)	32.9(4.9)	33.5(5.0)	33.9(3.2)	33(4.9)	33.3(4.8)	32.9(3.5)
Race- White	446 75.6)	249(68.4)	66(69.5)	297(77.1)	154(65.5)	47(69)[a]	244(79.2)	10(62.1)	31(62)[a]	193(73.9)	94(69.6)	19(70.4)
Black	11(1.9)	16(4.4)	1(1.1)[a]	8(2.1)	9(3.8)	3(4.4)	5(1.6)	4(2.3)	3(6)	5(1.9)	4(3)	0(0)
Asian/Native Hawaiian/Alaskan/Indian*	33(5.6)	30(8.2)	11(11.6)	23(6)	21(8.9)	3(4.4)	17(5.5)	16(9)	6(12)	19(7.3)	12(8.9)	3(11.1)
Mixed/Other race*	84(14.2)	60(16.5)	16(16.8)	43(11.2)	45(19.1)	14(20.6)	30(9.7)	40(22.6)	8(16)	32(12.3)	19(14.1)	4(14.8)
Hispanic ethnicity*- Non-Hispanic	447(75.8)	256(70.3)	64(67.4)[a]	306(79.5)	174(74)	49(72.1)	241(78.2)	128(72.3)	39(78)	200(76.6)	104(77)	23(85.2)
Hispanic	129(21.9)	105(28.8)	28(29.5)	65(16.9)	58(24.7)	17(25)	52(16.9)	44(24.9)	9(18)	46(17.6)	28(20.7)	3(11.1)
Education- High school or less	132(22.4)	146(40.1)	28(29.5)[a]	66(17.1)	72(30.6)	10(14)[a]	45(14.6)	52(29.4)	5(10)[a]	40(15.3)	32(23.7)	5(18.5)
≥ College education	458(77.6)	218(59.9)	67(70.5)	312(81)	162(68.9)	57(83.8)	255(82.8)	122(68.9)	43(86)	212(81.2)	101(74.8)	21(77.8)
Marital Status*- Not married/ partnered	197(33.4)	133(36.5)	3(3.2.)[a]	124(32.2)	94(40)	1(1.5)[a]	95(30.8)	77(43.5)	2(4)[a]	85(32.6)	50(37)	4(14.8)
Married/ partnered	393(66.6)	231(63.5)	92(96.8)	254(66)	140(59.6)	66(97.1)	205(66.6)	97(54.8)	46(92)	167(64)	83(61.5)	22(81.5)
Employment- Unemployed	131(22.2)	88(24.2)	18(18.9)	86(22.3)	50(21.3)	9(13.2)	70(22.7)	35(19.8)	6(12)	40(15.3)	29(21.5)	3(11.1)
Employed	454(76.9)	270(74.2)	77(81.1)	290(75.3)	180(76.6)	58(85.3)	228(74)	135(76.3)	42(84)	219(83.9)	106(78.5)	24(88.9)
Household Income- < $51,000	138(23.4)	122(33.5)	19(20)[a]	75(19.5)	67(28.5)	9(13.2)[a]	63(20.5)	55(31.1)	5(10)[a]	52(19.9)	39(28.9)	2(7.4)[a]
≥ $51,000	419(71)	212(58.2)	72(75.8)	283(73.5)	150(63.8)	55(80.9)	229(74.4)	111(62.7)	42(84)	199(76.2)	88(65.2)	23(85.2)
BMI*- <18.5	16(2.7)	13(3.6)	4(4.2)[a]	7(1.8)	11(4.7)	1(1.5)[a]	7(2.3)	6(3.4)	3(6)	5(1.9)	5(4.4)	1(3.7)
18.5-24.9	274(46.4)	134(36.8)	38(40)	180(46.8)	102(43.4)	29(42.6)	137(44.5)	80(45.2)	21(42)	116(44.4)	57(42.2)	12(44.4)
25-29.9	140(23.7)	81(22.3)	18(18.9)	94(24.4)	40(17)	21(30.9)	80(26)	29(16.4)	14(28)	67(25.7)	24(17.8)	6(22.2)
≥30	142(24.1)	125(34.3)	30(31.6)	89(23.1)	73(31.1)	13(19.1)	70(22.7)	53(29.9)	8(16)	60(23)	40(29.6)	6(22.2)
General Health*- Excellent	54(9.2)	34(9.3)	9(9.5)[a]	44(11.4)	22(9.4)	7(10.3)	37(12)	17(9.6)	4(8)	26(10)	11(8.1)	5(18.5)
Very Good	242(41)	119(32.7)	35(36.8)	163(42.3)	85(36.2)	28(41.2)	122(39.6)	67(37.9)	20(40)	106(40.6)	53(39.3)	8(29.6)
Good	241(40.8)	150(41.2)	35(36.8)	140(36.4)	99(42.1)	25(36.8)	114(37)	72(40.7)	18(36)	100(38.3)	56(41.5)	10(37)
Fair	45(7.6)	52(14.3)	16(16.8)	28(7.3)	24(10.2)	7(10.3)	23(7.5)	15(8.5)	6(12)	19(7.3)	10(7.4)	3(11.1)
Poor	7(1.2)	7(1.9)	0(0)	2(0.5)	4(1.7)	0(0)	3(1)	3(1.7)	0(0)	0(0)	3(2.2)	0(0)
Health Insurance- No insurance	21(3.6)	19(5.2)	6(6.3)	11(2.9)	10(4.3)	1(1.5)	7(2.3)	5(2.8)	2(4)	6(2.3)	5(3.7)	1(3.7)
Has insurance	569(96.4)	345(94.8)	89(93.7)	367(95.3)	224(95.3)	66(97.1)	293(95.1)	169(95.5)	46(92)	246(94.3)	128(94.8)	25(92.6)
Stress* - No/low stress	229(38.8)	115(31.6)	36(37.9)[a]	167(43.4)	73(31.1)	31(45)[a]	127(41.2)	61(34.5)	22(44)	106(40.6)	46(34.1)	10(37)
Moderate stress	325(55.1)	209(57.4)	52(54.7)	194(50.4)	141(60)	34(50)	160(51.9)	99(55.9)	23(46)	137(52.5)	75(55.6)	15(55.6)
High stress	36(6.1)	40(11)	7(7.4)	17(4.4)	20(8.5)	2(2.9)	13(4.2)	14(7.9)	3(6)	9(3.4)	12(8.9)	1(3.7)
Social Support(mean (SD))	4.3(0.8)	4.1(1.0)	4.4(0.7)[a]	4.3(0.8)	4.1(0.9)	4.5(0.7)	4.3(0.7)	4.1(1.0)	4.4(0.7)	4.2(0.8)	4.1(0.9)	4.3(0.7)
Cardiopulmonary comorbidities*- No	501(84.9)	307(84.3)	76(80)	332(86.2)	199(84.7)	54(79.4)	263(85.4)	143(80.8)	42(84)	219(83.9)	117(86.7)	21(77.8)
Yes	89(15.1)	57(15.7)	19(20)	46(11.9)	35(14.9)	13(19.1)	37(12)	31(17.5)	6(12)	33(12.6)	16(11.9)	5(18.5)
Psychological comorbidities- No	427(72.4)	258(70.9)	72(75.8)	282(73.2)	171(72.8)	49(72.1)	231(75)	131(74)	35(70)	195(74.7)	102(75.6)	18(66.7)
Yes	163(27.6)	106(29.1)	23(24.2)	96(24.9)	63(26.8)	18(26.5)	69(22.4)	43(24.3)	13(26)	57(21.8)	31(23)	8(29.6)
Endocrine comorbidities- No	476(80.7)	295(81)	70(73.7)	315(81.8)	181(77)	55(80.9)	250(81.2)	135(76.3)	39(78)	206(78.9)	104(77)	22(81.5)
Yes	114(19.3)	69(19)	25(26.3)	63(16.4)	53(22.6)	12(17.6)	50(16.2)	39(22)	9(18)	46(17.6)	29(21.5)	4(14.8)
Other comorbidities- No	412(69.8)	228(62.6)	69(72.6)[a]	255(66.2)	144(61.3)	50(73.5)	202(65.6)	106(59.9)	33(66)	161(61.7)	83(61.5)	18(66.7)
Yes	178(30.2)	136(37.4)	26(27.4)	123(31.9)	90(38.3)	17(25)	98(31.8)	68(38.4)	15(30)	91(34.9)	50(37)	8(29.6)
Parity- None	339(57.5)	208(57.1)	65(68.4)	385(100)	232(98.7)	66(97)[a]	306(99.4)	175(98.9)	48(96)	256(98.1)	134(99.3)	27(100)
≥1 Parity	251(42.5)	156(42.9)	30(31.6)	0(0)	3(1.3)	2(2.9)	2(0.6)	2(1.1)	2(4)	5(1.9)	1(0.7)	0(0)
Perceived Infertility Risk*- No increased risk	271(45.9)	99(27.2)	11(11.6)[a]	188(48.8)	59(25.1)	15(22)[a]	146(47.4)	53(29.9)	14(28)[a]	124(47.5)	38(28.1)	6(22.2)[a]
Increased risk	319(54.1)	265(72.8)	84(88.4)	197(51.2)	176(74.9)	53(77.9)	162(52.6)	124(70.1)	36(72)	137(52.5)	97(71.9)	21(77.8)

[§]Variables depicted as n(%) unless otherwise indicated; *Significant difference in proportion reporting attempting pregnancy across time points ($p < 0.05$); [a]Significant difference in proportion of attempting pregnancy between covariate groups at applicable time point ($p < 0.05$)

Table S3.4. Mean physical activity (standard deviation) over time by pregnancy intentions

Covariates	Baseline n=1049	6 Month n=688	1 Year n=535	1.5 Years n=423
Overall Cohort*	4.1 (2.0)	3.9 (2.0)	3.7 (1.9)	3.8 (1.9)
Pregnancy Intention Score				
0 (Don't want and not planning pregnancy)	4.0 (2.0)	4.0 (2.1)	3.8 (2.0)	3.8 (1.9)
0.5 (Don't want now but planning later)	4.1 (2.1)	2.4 (1.4)	2.9 (1.2)	4.7 (1.7)
1 (Want but not planning pregnancy)	4.2 (2.2)	4.4 (2.1)	3.8 (1.9)	4.4 (2.4)
1.5 (Want and planning later)	3.9 (1.9)	3.8 (1.9)	3.7 (1.9)	3.8 (1.9)
2 (Want and planning now)	4.5 (1.9)	4.2 (2.1)	3.7 (2.0)	3.9 (1.9)
Trying*				
Not trying	4.0 (1.9)	3.8 (1.9)	3.7 (1.8)	3.8 (2.0)
Neither	4.1 (2.1)	4.0 (2.1)	3.7 (2.0)	3.9 (2.0)
Trying now	4.6 (1.8)	4.4 (2.3)	4.0 (2.0)	4.1 (2.0)

* Significant difference in PA across time points ($p < 0.05$)

Table S3.5. Distribution of smoking (n (%)) over time by pregnancy intentions

	Baseline		6 Month		1 Year		1.5 Years	
	Non-smoker n=976	Smoker n=64	Non-smoker n=656	Smoker n=28	Non-smoker n=514	Smoker n=16	Non-smoker n= 406	Smoker n= 16
Pregnancy Intention Score								
0 (Don't want & not planning)	280 (28.7)	26 (40.6)	203 (30.9)	10 (35.7)	168 (32.47)	4 (25.0)	155 (38.2)	4 (25.0)
0.5 (Don't want now but planning later)	24 (2.5)	3 (4.7)	12 (1.8)	0 (0)	12 (2.3)	0 (0)	6 (1.5)	1 (6.2)
1 (Want but not planning)	87 (8.9)	8 (12.5)	55 (8.4)	5 (17.9)	46 (8.9)	5 (31.2)	32 (7.9)	3 (18.8)
1.5 (Want and planning later)	364 (37.3)	20 (31.2)	228 (34.8)	8 (28.6)	165 (32.1)	5 (31.2)	119 (29.3)	5 (31.2)
2 (Want and planning now)	177 (18.4)	7 (10.9)	127 (19.4)	4 (14.3)	101 (19.6)	2 (12.5)	73 (18.0)	3 (18.8)
Trying								
Not trying	562 (57.6)	28 (43.8)[a]	372 (56.7)	12 (42.9)	299 (58.2)	8 (50.0)	251 (61.8)	9 (56.2)
Neither	324 (33.2)	34 (53.1)	219 (33.4)	15 (53.6)	166 (32.3)	7 (43.8)	129 (31.8)	6 (37.5)
Trying now	90 (9.2)	2 (3.1)	65 (9.9)	1 (3.6)	49 (9.5)	1 (6.2)	26 (6.4)	1 (6.2)

*Significant difference in smoking across time points ($p < 0.05$)
[a]Significant difference in smoking between groups at applicable time point ($p < 0.05$)

Table S3.6. Mixed effects models of the association of changes in pregnancy intention score (PIS) (left) and trying to become pregnant (right) with physical activity and smoking stratified by perceived infertility risk

	Physical Activity				Smoking			
	PIS[a]		Trying[b]		PIS[c]		Trying[d]	
	Adjusted B(95% CI)	p	Adjusted B(95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
No perceived infertility risk								
Multiple Imputation Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	References		References	
Decreased Intention	0.2 (-0.2, 0.7)	0.3	0.02 (-0.5, 0.5)	0.9	1.7 (0.3, 8.5)	0.5	0.3 (0,0)	1
Increased Intention	0.4 (-0.03, 0.9)	0.06	0.2 (-0.2, 0.6)	0.3	2.1 (0.2, 9.6)	0.7	0.2 (0,0)	**1**
Random Effects	1.5							
Complete Cases Model- Fixed Effects								
No Change in Intention	Reference	**-**	Reference	-	References		References	
Decreased Intention	0.03 (-0.2, 0.3)	0.92	-0.01 (-0.3, 0.2)	0.9	4.3 (0.3, 69.5)	0.3	0	
Increased Intention	0.33 (0.1, 0.6)	**0.01**	0.2 (-0.03, 0.5)	0.07	0.5 (0.01, 30.4)	0.7	0	
Random Effects	1.5		1.5		3.3		3.3	
Perceived infertility risk								
Multiple Imputation Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	References		References	
Decreased Intention	0.02 (-0.3, 0.3)	0.9	0.1 (-0.1, 0.5)	0.3	1.4 (0.5, 3.7)	0.5	2.58 (1.2, 5.7)	**0.02**
Increased Intention	0.03 (-0.3, 0.4)	0.8	0.2 (-0.2, 0.6)	0.3	1.3 (0.4, 4.0)	0.6	1.12 (0.4, 2.8)	0.8
Random Effects	1.7		1.5					
Complete Cases Model- Fixed Effects								
No Change in Intention	Reference	**-**	Reference	-	References		References	
Decreased Intention	-0.03 (-0.2, 0.1)	0.7	0.1 (-0.04, 0.3)	0.13	2.4 (0.4, 13.9)	0.3	4.6 (0.9, 25.0)	0.07
Increased Intention	0.06 (-0.1, 0.2)	0.5	0.2 (-0.01, 0.3)	0.06	1.4 (0.2, 10.9)	0.7	0.7 (0.07, 6.3)	0.7
Random Effects	1.7		1.7		3.3		3.3	

[a] Model adjusted for time, race, ethnicity, age at baseline, education, BMI, general health, stress, social support, perceived infertility risk
[b] Model adjusted for time, race, ethnicity, age at baseline, education, employment, household income, BMI, general health, stress, perceived infertility risk
[c] Model adjusted for time, age at enrollment, race, ethnicity, education, marital status, employment, income, BMI, general health, presence of insurance, stress, social support, comorbidities, parity, perceived infertility risk
[d] Model adjusted for time, race, ethnicity, employment, income, perceived infertility risk

Table S3.7. Mixed effects models of the association of changes in pregnancy intention score (PIS) (left) and trying to become pregnant (right) with physical activity and smoking, stratified by parity

	Physical Activity				Smoking			
	PIS[a]		Trying[b]		PIS[c]		Trying[d]	
	Adjusted B(95% CI)	p	Adjusted B (95% CI)	p	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
Nulliparous								
Multiple Imputation Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	Reference		Reference	
Decreased Intention	0.02 (-0.2, 0.3)	0.9	0.1 (-0.2, 0.4)	0.5	1.4 (0.5, 3.7)	0.5	2.9 (1.0, 8.6)	0.05
Increased Intention	-0.03 (-0.3, 0.3)	0.8	0.2 (-0.1, 0.5)	0.2	0.8 (0.2, 2.8)	0.7	0.8 (0.2, 2.8)	0.7
Random Effects								
Complete Cases Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	Reference		Reference	
Decreased Intention	-0.02 (-0.2, 0.2)	0.8	0.1 (-0.1, 0.3)	0.6	1.5 (0.2, 12.7)	0.7	6.9 (0.9, 49.6)	0.05
Increased Intention	-0.01 (-0.2, 0.2)	0.8	0.2 (-0.03, 0.3)	0.1	0.5 (0.04, 6.3)	0.6	0.2 (0.01, 7.5)	0.4
Random Effects	1.8		1.8		3.3		3.3	
Parous								
Multiple Imputation Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	References		References	
Decreased Intention	0.1 (-0.3, 0.5)	0.6	0.3 (-0.1, 0.8)	0.1	1.6 (0.6, 4.5)	0.3	0.8 (0.2, 3.5)	0.8
Increased Intention	0.6 (0.1, 1.1)	**0.02**	0.2 (-0.2, 0.6)	0.4	1.6 (0.4, 6.1)	0.4	0.9 (0.2, 3.7)	0.8
Random Effects								
Complete Cases Model- Fixed Effects								
No Change in Intention	Reference	-	Reference	-	References		References	
Decreased Intention	0.04 (-0.2, 0.3)	0.7	0.1 (-0.1, 0.3)	0.2	4.5 (0.5, 44.7)	0.5	0.7 (0.03, 18.2)	0.8
Increased Intention	0.47 (0.2, 0.7)	**0.001**	0.3 (0.03, 0.5)	**0.02**	2.6 (0.2, 44.3)	0.5	1.3 (0.1, 20.6)	0.8
Random Effects	1.3		1.4		3.3		3.3	

[a] Model adjusted for time, race, ethnicity, age at baseline, education, BMI, general health, stress, social support, perceived infertility risk
[b] Model adjusted for time, race, ethnicity, age at baseline, education, employment, household income, BMI, general health, stress, perceived infertility risk
[c] Model adjusted for time, age at enrollment, race, ethnicity, education, marital status, employment, income, BMI, general health, presence of insurance, stress, social support, comorbidities, parity, perceived infertility risk
[d] Model adjusted for time, race, ethnicity, employment, income, perceived infertility risk

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CHAPTER 4

Perceptions and objective measures of infertility risk in female adolescent and young adult cancer survivors

ABSTRACT

Purpose: To assess the association of treatment gonadotoxicity and menstrual patterns with infertility risk perception among female adolescent and young adult (AYA) cancer survivors. To evaluate the agreement between infertility risk perception and objective ovarian function.

Methods: Cross-sectional analyses was conducted with data collected between 2013-2017 from 785 female AYA survivors aged 18-39 years, who completed primary cancer treatment, did not undergo hysterectomy, and enrolled in an ovarian function study. Participants completed surveys assessing infertility perception and frequency of menstruation. Gonadotoxicity of cancer treatments was identified through medical abstraction and ovarian reserve was assessed by biomarkers collection. Multivariable logistic regressions evaluated associations with perceived infertility risk and with discordant risk estimation between perceived and objective infertility risk.

Results: Participants exposed to moderate and high gonadotoxic treatments had higher odds of perceiving infertility risk compared to exposure to low gonadotoxic treatments (adjusted Odds Ratio (aOR) [95%CI]: 2.3[1.2, 4.4] and 16 [4.6, 52.9], respectively). Amenorrhea was associated with higher odds of perceiving increased infertility risk compared to regular cycles (aOR [95% CI] 3.4 [1.7, 6.8]). Objective infertility risk had minimal agreement (κ=0.19) with perceived infertility risk. Cancer type, parity, age, high fertility concern, and previous infertility were associated with discordant risk estimation.

Conclusions: Fertility concerns post-cancer treatment are associated with cancer treatments and amenorrhea. AYA survivors did not accurately estimate their infertility risk. This study supports the need for age appropriate and repeated fertility counseling.

INTRODUCTION

Infertility in female adolescent and young adult (AYA) cancer survivors can stem from depletion of the finite ovarian reserve, disruption of hypothalamic-pituitary-ovarian function, and/or injury to the uterus.[1] AYA survivors experience higher rates of infertility and lower rates of pregnancy and live birth, compared to rates reported for both siblings without cancer and childhood cancer survivors.[2,3] Although many AYA survivors retain the potential to have children post-cancer, infertility concerns cause significant psychological distress, and misperceptions about fertility potential can lead to unplanned pregnancies and/or misinformed reproductive decisions.[4–6]

Fertility perceptions and their alignment with objective risk are understudied among AYA survivors. Previous studies, largely in childhood cancer survivors, report that survivors often over- or under-estimate their infertility risk.[2,7–9] A recent study by Lehmann et al. found 49% of female survivors misperceived their infertility risk when compared to their objective gonadal function.[10] Another review of adult women with chronic conditions, including cancer, found women do not accurately assess the impact of their condition on fertility.[11] Studies show 44-50% of AYA survivors report high reproductive concerns[12,13], but little is known about factors associated with infertility risk perception and how perceived risk compares to objective risk. Identifying characteristics associated with infertility risk perceptions and assessing the accuracy of perceptions may identify survivors needing greater fertility counseling support.

This study has two objectives. First, the study aimed to estimate the association of treatment gonadotoxicity and menstrual patterns with infertility risk perception among female AYA survivors. Treatment gonadotoxicity is associated with infertility risk perception in childhood survivors.[10] Lack of or irregular menstrual patterns inform fertility perception among general populations of women and menstrual history is considered a vital sign of overall health for adolescent women.[14–16] We hypothesized that increased treatment gonadotoxicity or irregular

menstrual pattern will be associated with higher infertility risk perception. Second, the study aimed to evaluate the agreement between infertility risk perception and objective ovarian function. We hypothesized that similar to childhood cancer survivors[10], female AYA survivors' infertility risk perception will have poor agreement with objective ovarian function measures.

METHODS

This cross-sectional study used baseline data collected between 2013-2017 from the Reproductive Window in Young Adult Cancer Survivors (Window) study, a longitudinal study to estimate the trajectory of ovarian function among AYA survivors.[17] Participants were recruited through California and Texas cancer registries, social media, and physician referrals. Eligibility criteria included females 18-39 years old, diagnosed with AYA cancer between 15-39 years of age, completed primary cancer treatment, and had at least one ovary. Exclusion criteria were uncontrolled endocrinopathies and multiple cancers or recurrence. More than 30,000 recruitment letters were sent to potentially eligible individuals identified by the California and Texas cancer registries, social media, and physician referrals. Of this group n=1825 contacted the study team and were assessed for eligibility, 1269 were eligible, and 1159 consented to the study. A total of 1071 eligible participants completed baseline surveys and were included within the Window study. For this analysis, participants who completed baseline surveys, had complete medical record abstraction of oncology treatments, and did not undergo hysterectomy were included. The State of California Committee for the Protection of Human Subjects and the Institutional Review Boards at the University of California, San Diego, and the Texas Department of State Health Services approved the study.

Data Collection

Participants self-reported their demographic information, medical history, reproductive history and menstrual pattern via an online questionnaire. Cancer diagnosis and treatment data were abstracted by 2 board-certified pediatric oncologists and 1 board-certified reproductive endocrinologist using the Childhood Cancer Survivor Study methods.[18] A high agreement was reported on re-review of 25% of the abstracted data.[19]

Dried blood spots (DBS) for measuring endocrine biomarkers were self-collected by participants and shipped to the research team.[19] Menstruating participants collected DBS in the early follicular phase (cycle days 3-7); amenorrheic participants collected DBS on a random day. Once received, DBS samples were inspected for quality and frozen at -80°C.

Measures

Perceived infertility risk. Participants were asked "How do you feel about your own fertility (ability to get pregnant) right now" in comparison to females their age. Responses included: I feel I am more fertile, I think I am as fertile, I think I am less fertile, and I think I am unable to get pregnant.[6] Responses were collapsed to compare any perception of increased infertility risk to no perception of increased risk. Final categories were: no increased risk (included same or more fertile) and increased risk (less fertile or unable to get pregnant).

Gonadotoxicity of cancer treatments. Cancer treatments were categorized into three groups: low-, moderate-, and high gonadotoxicity. Categorization was determined by literature review and clinician input on the level of toxic effect induced on ovarian function.[20–25] High toxicity treatments included: any pelvic radiation, stem cell or bone marrow transplants (autologous or allogeneic), or cyclophosphamide equivalent dose (CED) of ≥7 grams/m^2). Low toxicity treatments included surgery only (excluding unilateral oophorectomy), endocrine therapy only, radioiodine treatment, and cervical trachelectomy. All remaining exposures were classified

as moderate toxicity. These included: biologics, platinums, ABVD, HIPEC, unilateral oophorectomy, trachelectomy, CED <7 grams/ m^2, and bevacizumab.

Ovarian function. Number of menses in the past year and cycle variations in bleeding pattern were used to categorize menstrual pattern.[19,26] Participants who were not on hormonal birth control within the past year were categorized as having regular, irregular or no menstrual cycles. Participants reporting 10-12 menses in the last year without inter-bleeding intervals of more than 60 days apart were categorized as having regular menstrual cycles.[26] Participants who reported ≤9 menses in the past year were categorized as having irregular menstrual cycles. Participants reporting amenorrhea in the past year included those who never experienced menarche.

DBS is valid and reliable for the detection of antimüllerian hormone (AMH) and follicle-stimulation hormone (FSH).[27,28] AMH and FSH levels were assessed through enzyme-linked immunosorbent assays (ELISAs) designed specifically for DBS samples (Limit of detection 0.03 ng/mL and 0.07 mIU/mL, respectively, and inter-assay and intra-assay coefficient of variation < 10%) (AL-129, AL-187, Ansh Labs, Webster TX).[19] We excluded AMH and FSH levels collected within two years of treatment because of known ovarian function recovery during this time period in order to reduce misclassification based on acute effect of cancer treatment. We excluded FSH levels in females on hormonal therapy. AMH <1 ng/mL and FSH > 10 IU/L were considered evidence of impaired fertility.[19,29]

Confounders. Potential confounders were selected through literature review on factors associated with infertility risk perceptions among childhood cancer survivors and general populations of women. Demographic variables included age, race, ethnicity, sexual orientation, education, income, marital status, and health insurance coverage. Respondents ranked their overall general health with 5 responses from excellent to poor. Body mass index (BMI) was

calculated with self-reported weight and height. Self-reported comorbidities were categorized as cardiovascular/pulmonary, endocrine, psychological, and other comorbidities. Psychosocial factors included stress measured by the Perceived Stress Scale-10[30], depression measured by the Patient Health Questionnaire depression scale[31], and social support by RAND institutes medical outcomes study survey.[32] Concerns about fertility potential and becoming pregnant were assessed utilizing subscales from the Reproductive Concerns after Cancer (RCAC) scale.[12,33] Responses in each domain were captured on a 5-point likert scale and then averaged within each domain. A higher score indicates a greater level of concern within each scale.

Statistical Analysis

All analyses were conducted with R Studio Version 1.2.5001. On factors associated with perceived infertility risk, the exposures of interest were gonadotoxicity of cancer treatments and menstrual pattern over the prior 12 months. Following descriptive analysis, bivariable analyses estimated associations between exposures and outcomes using chi-square, Fisher's Exact and Student's t-test, as appropriate. Covariates closely associated with one another (Rho ≥0.5) were reduced to include one of the two variables in the final model. Binomial logistic regression was utilized in multivariable analyses. The model was built as an explanatory model in which all covariates were included and then reduced if non-significant in the model and did not present confounding (≤ 10% change in parameter).

Accurate perception of infertility risk was assessed by the percent agreement and strength of correlation with objective infertility risk. Participants were categorized as having impaired fertility (or not) based on treatment gonadotoxicity and measures of ovarian function (Supplemental Figure 1). First, participants were categorized into impaired fertility if they were exposed to moderate or high gonadotoxicity treatments regardless of menstrual pattern and ovarian reserve test. Among those exposed to low gonadotoxicity treatments, those with low AMH, high FSH, or irregular or no menstrual cycles were categorized as impaired fertility. Within

the low gonadotoxicity treatment exposure group, females on hormone therapy and who did not have AMH levels could not be classified. Cohen's kappa statistic was utilized to evaluate the strength of correlation between measures. Agreement between ovarian function and perceived infertility risk was classified as: accurate, underestimate or overestimate of risk. Characteristics associated with risk assessment were assessed with multinomial regression model. Per an explanatory model process all covariates identified as potentially associated were included and then reduced if non-significant.

RESULTS

A total of 785 participants from the parent study (n=1,071) were included (Table 1). Of the 1071 from the parent study who completed baseline surveys, n=268 (25%) did not complete medical chart abstraction and n=18 were excluded due to undergoing a hysterectomy. Participants who were excluded due to no medically abstracted information were more likely to be Hispanic, parous, and report worse general health, and less likely to complete college and have breast cancer ($p<0.05$). Most participants were White (74.5%), non-Hispanic (78%), married (69.9%) and completed college (77.1%). Categorized by cancer treatment exposure, 29%, 61%, and 10% of participants received low, moderate, and high gonadotoxicity treatments, respectively. Forty percent of participants reported regular menstrual pattern, 46% reported irregular menstrual cycles, and 14% were amenorrheic. A majority of participants (61.5%) perceived increased risk of infertility; 38.9% (n=306) reported they were less fertile and 22.6%(n=177) considered themselves infertile compared to peers their age. Only 3.5% (n=27) of participants perceived themselves to be more fertile and 35% (n=275) perceived themselves as fertile as their peers.

Treatment gonadotoxicity, menstrual pattern and perceived infertility risk

In bivariable analysis, treatment gonadotoxicity and menstrual pattern were associated with perceived infertility risk (Table 1). Comorbidities, cancer type and proximity to treatment, and reproductive characteristics were also associated with perception of infertility risk.

Due to multicollinearity, age at enrollment and stress were retained in all multivariable models, while age at diagnosis and depression was removed. Moderate and high gonadotoxicity treatment exposures were associated with increased perceived infertility risk compared to low gonadotoxicity treatment (Table 2). Compared with participants exposed to low gonadotoxicity treatments, those exposed to moderate gonadotoxicity treatments had a 2.3 fold higher odds (95% CI 1.2, 4.4) of perceiving increased risk of infertility, while those exposed to high gonadotoxicity treatments had a 16 fold higher odds (95% CI 4.6, 52.9) of perceiving increased risk.

Amenorrhea, but not irregular menstrual cycles, was significantly associated with higher odds of perceiving increased infertility risk (aOR 3.4, 95% CI 1.7, 6.8) (Table 2). In adjusted analysis, history of parity was associated with no increased perception of infertility risk.

Agreement between objective and perceived infertility risk

Sixty percent (n=475) of participants were categorized as having objective infertility risk while 22.8% (n=179) were categorized as not having objective infertility risk; 16.6% (n= 131) could not be categorized due to lack of ovarian reserve testing while on hormonal therapy. Overall, 64% of participants accurately assessed risk, 12.7% overestimated risk, and 23.5% underestimated risk (Table 3). Objective infertility risk had minimal agreement (κ=0.19) with perceived infertility risk.

No variables were identified that were associated with overestimating risk, while compared to thyroid cancer survivors, breast and skin cancer survivors were less likely to overestimate risk (aOR 0.2, 95% CI 0.1, 0.5 and aOR 0.4, 95%CI 0.1, 0.7, respectively) (Table 4). Parous participants had 2.8 higher odds (95%CI 1.7, 4.6) of underestimating risk compared

to nulliparous participants. Factors associated with lower odds of underestimating risk included: age, endocrine comorbidities, surviving gastrointestinal cancer, high fertility concern, and previous infertility.

DISCUSSION

This study aimed to characterize factors associated with fertility perceptions and to contextualize the agreement between perception and objective infertility risk among female AYA cancer survivors. Previous studies on characteristics associated with fertility perception and accurate estimation of risk are limited to childhood cancer survivors.[7–10] This study found both higher gonadotoxicity of cancer treatment and amenorrhea were associated with higher odds of infertility risk perception. Additionally, survivors perceived risk was in poor agreement with objective infertility risks based on Cohen's kappa statistic criteria. Female AYA survivors, especially those who experience higher gonadotoxic treatment and/or experience amenorrhea, are in need of improved fertility guidance.

As hypothesized treatment gonadotoxicity was associated with higher odds of increased infertility risk perceptions. Previous studies have shown AYA survivors have limited recall on specifics of their treatment but are able to accurately recall general exposures such as yes/no on receiving chemotherapy.[34] This may explain why higher gonadotoxic treatments were associated with risk perception but only minimal agreement was seen between perception and objective risk determined by treatment gonadotoxicity. AYAs may have a general idea of treatment impact on their fertility but are unclear about the specific risks. Low recall and knowledge of treatments are common among childhood cancer survivors where treatments like bone marrow transplant are associated with infertility worry but gonadotoxic radiation and chemotherapy are not consistently associated.[9,10] AYA survivors are in need of tailored

education on their specific treatment, type of chemotherapy utilized, and the subsequent acute or long-term effects on fertility.

To the best of our knowledge, no studies have examined the impact of menstrual pattern on infertility risk perceptions among cancer survivors despite menstrual pattern as a marker for potential fertility issues.[14,15] Menstruation is a vital sign of health because early detection of abnormal patterns can identify future reproductive concerns.[16] As expected, amenorrhea was positively associated with infertility risk perception but unexpectedly irregular cycles were not. Among general populations of women, regular menstruation is part of "normal" bodily function and any irregularity is cause for concern, even when using contraceptives that purposefully affect regular menstruation.[14,35–37] Lack of significant association between irregular cycles and perceptions may indicate survivor gap in knowledge of either an irregular cycle or its potential indication for ovarian issues. Menstruation alone is not sufficient to accurately assess fertility among female AYA survivors, without ovarian reserve biomarkers irregular patterns may misclassify reproductive age staging.[19] In this study, among participants who received higher gonadotoxic treatments, 37.7% (n=126) had normal biomarkers but irregular/ no periods. Both treatment knowledge and current menstrual patterns are important in informing infertility risk and concern among survivors.[19]

This study found minimal agreement between perceptions of infertility risk when compared to risk assessed by ovarian function. Although, 64% of participants accurately assessed fertility risk a Cohen's kappa requires ≥80% to qualify a strong agreement.[38] A similar kappa (κ =0.19) was found in a study among childhood survivors between perceived and gonadal function defined fertility risk. One study among AYA survivors of childhood cancer found moderate agreement (κ=0.66) between FSH measured and self-reported premature ovarian insufficiency and even greater agreement among survivors who repeatedly interacted with survivorship clinics or endocrinologists (κ=0.83 & κ=1.0, respectively).[7] The current study was limited in assessing how much interaction and counseling survivors received from

survivorship clinics or endocrinologists. Any past visit with a fertility specialist was assessed but was not significantly associated with perceived infertility risk. It is known AYA survivors face barriers when transitioning between pediatric and adult care and often surveillance of long-term effects falls on general practitioners who may be unfamiliar with survivor care.[7,39] Repeated counseling from specialists may improve knowledge of late cancer effects on fertility.

A significant strength of this study is the use of three objective measures of infertility risk: cancer treatment gonadotoxicity, menstrual pattern, and ovarian reserve markers. The use of AMH and FSH in combination with hormonal therapy and menstrual pattern allowed for better estimation of ovarian function and follows clinical recommendations for AYA survivors.[19,40] Other studies mainly utilized treatment gonadotoxicity to estimate impaired fertility and only a few included biomarkers but often only FSH. [7–9] AMH is consistent throughout menstrual cycles even when on hormonal contraception, whereas FSH can fluctuate and requires specific timing for accurate assessment of ovarian function.[41] Another strength of this study was a sufficient sample size of female AYA survivors to assess associations with both under and overestimation of risk. Although participants were recruited from population-based cancer registries, fertility, and oncology clinics, low response rate may indicate potential selection bias of survivors interested in a study on reproductive health after cancer.

Fertility information post cancer treatment continues to be an unmet need for AYA survivors.[42,43] Past studies have established fertility concerns post-cancer treatment are a significant source of psychological distress and lowered quality of life among AYA survivors.[12,44] Age appropriate and repeated fertility counseling throughout survivorship care can help reduce concerns and misperceptions around fertility. Survivors who experienced high gonadotoxic treatments or experience amenorrhea may be particularly susceptible to psychological burden and distress. Past studies with AYA survivors show the use of survivorship care plans can lower infertility concerns and reduce unmet information needs.[13,45] However survivorship care plans may not always be available and components of these plans may not include fertility focused

follow-up care. Strategies to reduce misalignment between perceptions and actual risk are essential to reducing psychological distress and improving quality of life for AYA survivors.

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Table 4.1 Demographic, cancer, and fertility characteristics of female AYA cancer survivors by perceived infertility risk

Covariates[1]	Total Sample n=785	Perceived Infertility Risk: Not increased n=302	Perceived Infertility Risk: Increased n=483	p value
Treatment Gondatoxicity- Low	225 (28.7)	125 (41.4)	100 (20.7)	**<0.001**
Moderate	479 (61)	173 (57.3)	306 (63.4)	
High	81 (10.3)	4 (1.3)	77 (15.9)	
Menstrual Pattern- Regular Periods	316 (40.3)	158 (52.3)	158 (32.7)	**<0.001**
No Periods	109 (13.9)	19 (6.3)	90 (18.6)	
Irregular Periods	360 (45.9)	125 (41.4)	235 (48.7)	
Age at enrollment (mean (SD))	33.2 (4.8)	33.6 (4.6)	33.0 (4.9)	0.13
Age at diagnosis (mean (SD))	25.9 (5.7)	25.4 (5.6)	26.2 (5.7)	**0.06**
Race- White	585 (74.5)	230 (76.2)	355 (73.5)	0.48
Black	23 (2.9)	8 (2.6)	15 (3.1)	
Asian/Native Hawaiian/Native Alaskan/Native	54 (6.9)	21 (7.0)	33 (6.8)	
Mixed/Other race	108 (13.8)	34 (11.3)	74 (15.3)	
Hispanic Ethnicity	167 (21.3)	60 (19.9)	107 (22.2)	0.53
Heterosexual	735 (93.6)	283 (93.7)	452 (93.6)	1
Relationship status: married/ living	546 (69.9)	218 (72.2)	328 (67.9)	0.21
≥ College education	605 (77.1)	241 (79.8)	364 (75.4)	0.18
Employed	609 (77.6)	242 (80.1)	367 (76.0)	0.34
Household Income ≥$51,000	551 (70.2)	232 (76.8)	319 (66.0)	**0.003**
Has health insurance	760 (96.8)	295 (97.7)	465 (96.3)	0.38
BMI- <18.5	34 (3.1)	10 (3.3)	14 (2.9)	0.63
18.5-24.9	363 (46.2)	135 (44.7)	228 (47.2)	
25-29.9	178 (22.7)	75 (24.8)	103 (21.3)	
≥30	198 (25.2)	72 (23.8)	126 (26.1)	
General Health- Excellent	82 (10.4)	37 (12.3)	45 (9.3)	**0.01**
Very Good	325 (41.4)	134 (44.4)	191 (39.5)	
Good	296 (37.7)	112 (37.1)	184 (38.1)	
Fair/ Poor	80 (10.2)	18 (6.0)	62 (12.8)	
Cardiovascular/Pulmonary Comorbidities	115 (14.6)	35 (11.6)	80 (16.6)	0.07
Endocrine Comorbidities	148 (18.9)	43 (14.2)	105 (21.7)	**0.01**
Psychological Comorbidities	204 (26.0)	66 (21.9)	138 (28.6)	**0.04**
Other Comorbidities	265 (33.8)	104 (34.4)	161 (33.3)	0.81
Stress- No/low stress	313 (39.9)	135 (44.7)	178 (36.9)	**0.003**
Moderate stress	423 (53.9)	158 (52.3)	265 (54.9)	
High stress	49 (6.2)	9 (3.0)	40 (8.3)	
Depression- No significant depression	226 (28.8)	76 (25.2)	150 (31.1)	0.22
Mild	105 (13.4)	35 (11.6)	70 (14.5)	
Moderate	42 (5.4)	13 (4.3)	29 (6.0)	
Moderately severe/ Severe	12 (1.5)	3 (1.0)	9 (1.9)	
Social Support (mean (SD))	4.3 (0.8)	4.3 (0.8)	4.3 (0.8)	0.51
Cancer Type- Thyroid	154 (19.6)	77 (25.5)	77 (15.9)	**<0.001**
Breast	209 (26.6)	71 (23.5)	138 (28.6)	
Blood/ Leukemia/Lymphoma	268 (34.1)	93 (30.8)	175 (36.2)	
Reproductive (cervix, uterus, ovary)	58 (7.4)	17 (5.6)	41 (8.5)	
Gastrointestinal	23 (2.9)	7 (2.3)	16 (3.3)	
Bone/ Soft tissue	49 (6.2)	19 (6.3)	30 (6.2)	
Skin	24 (3.1)	18 (6.0)	6 (1.2)	
Years since treatment completion- 0-2	44 (5.6)	12 (4.0)	32 (6.6)	**0.01**
3-4 years	140 (17.8)	45 (14.9)	95 (19.7)	
5-8 years	326 (41.5)	119 (39.4)	207 (42.9)	
≥ 9 years	275 (35.0)	126 (41.7)	149 (30.8)	
Ever ≥1 Parity	297 (37.8)	163 (54.0)	134 (27.7)	**<0.001**
Reproductive Concerns After Cancer Scale (RCAC)- Fertility potential domain	3.3 (1.3)	2.5 (1.2)	3.8 (1.0)	**<0.001**
RCAC- Becoming pregnant domain (mean	2.8 (1.0)	2.6 (1.0)	2.9 (1.0)	**<0.001**
Ever visited fertility specialist	248	60(19.9)	188 (38.9)	**<0.001**

Table 4.1 Demographic, cancer, and fertility characteristics of female AYA cancer survivors by perceived infertility risk **Continued**

Covariates[1]	Total Sample n=785	Perceived Infertility Risk: Not increased n=302	Perceived Infertility Risk: Increased n=483	p value
Ever received fertility treatment	99 (12.6)	28 (9.3)	71 (14.7)	**0.03**
Ever previous infertility	108 (13.8)	15 (5.0)	93 (19.3)	**<0.001**
Hormone Therapy/ Medication (last 12	356 (45.4)	110 (36.4)	246 (50.9)	**<0.001**

[1] Variables depicted as n(%) unless otherwise indicated

Table 4.2 Unadjusted and adjusted models of the association of treatment gonadotoxicity with perceived infertility risk

	Perceived Infertility Risk	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Treatment Gonadotoxicity[1]		
Low	Reference	Reference
Moderate	2.18 (1.58, 3.01)	2.32 (1.22, 4.41)
High	21.59 (8.09, 54.62)	15.67 (4.64, 52.90)
Menstrual Pattern		
Regular Periods	Reference	Reference
Irregular Periods	1.69 (1.23, 2.31)	1.40 (0.95, 2.06)
No Periods	2.73 (1.55, 4.79)	3.39 (1.68, 6.84)
Endocrine Comorbidities	2.24 (1.47, 3.41)	2.14 (1.28, 3.58)
Ever ≥1 Parity	0.33 (0.24, 0.45)	0.44 (0.29, 0.67)
Reproductive Concerns After Cancer Scale- Fertility potential domain	2.50 (2.15, 2.90)	2.29 (1.92, 2.72)
Ever Previous Infertility	4.76 (2.69, 8.43)	6.57 (3.29, 13.11)

Abbreviations: OR- Odds Ratio, 95% CI- 95% confidence interval

[1] Following variables were not significant at $p<0.05$ in adjusted model: race, ethnicity, sexual orientation, relationship status, college education, employment, household income, health insurance, general health, BMI, cardiovascular/pulmonary comorbidities, psychological comorbidities, other comorbidities, stress, social support, years since treatment, completion Reproductive Concerns After Cancer Scale - becoming pregnant domain, ever received fertility treatment, hormone therapy/ medication (last 12 months)

Table 4.3 Strength of agreement/disagreement between perceptions of infertility risk with objective measures of infertility risk

	Ovarian Function[1] (n (%))		
	No Impaired fertility	Impaired Fertility	Weighted Cohen's κ
	n= 179	**n=475**	
Perceived Infertility Risk			0.19
No increased risk	96 (14.7)	154 (23.5)	
Increased Risk	83 (12.7)	321 (49.1)	

[1]Gondal functioning category definitions see Figure 1.

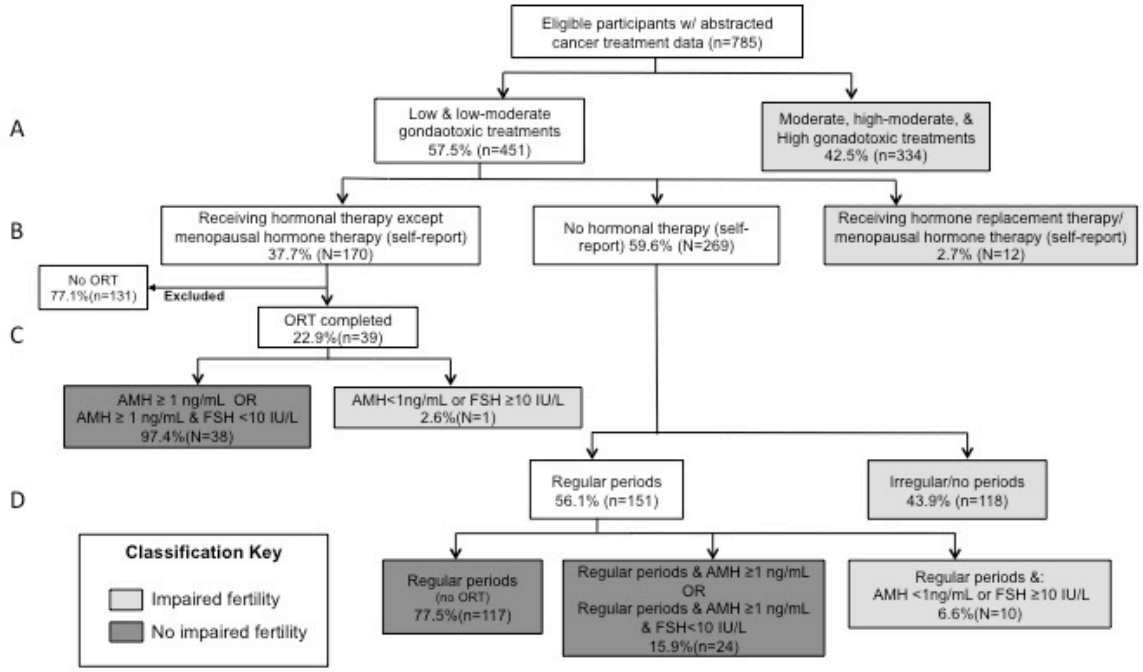
Table 4.4 Multivariable model of the association between demographic, cancer, and fertility characteristics covariates and underestimation of risk between perceived infertility risk and current gonadal function (reference= accurate agreement of infertility risk)

	Accurate Estimation of Risk	Underestimate (No Perceived Risk & Impaired Gonadal Function		Overestimate (Perceived Risk & No Impaired Gonadal Function)	
	n=321	n=154		n=83	
Covariates[1]	% (n)	% (n)	OR (95% CI)	% (n)	OR (95% CI)
Age at enrollment (mean (SD))	33.5 (4.8)	33.3 (4.8)	0.9 (0.8, 0.9)*	33.9 (4.5)	1.1 (1.0, 1.1)
Ever ≥1 Parity	37.2 (155)	59.1 (91)	2.8 (1.7, 4.6)*	27.7 (23)	0.5 (0.3, 1.0)
Endocrine Comorbidities	78 (18)	8.4 (13)	0.4 (0.2, 0.7)*	27.7 (23)	1.2 (0.7, 2.2)
Cancer Type					
Thyroid	13.2 (55)	18.2 (28)	-	30.1 (25)	-
Breast	30.2 (126)	30.5 (47)	0.8 (0.4, 1.5)	16.9 (14)	0.2 (0.1, 0.5)*
Blood/ Leukemia/Lymphoma	36.7 (153)	35.1 (54)	0.4 (0.2, 1.2)	32.5 (27)	0.6 (0.3, 1.6)
Reproductive (cervix, uterus, ovary)	7.4 (31)	4.5 (7)	0.4 (0.1, 1.7)	10.8 (9)	0.4 (0.1, 1.9)
Gastrointestinal	2.9 (12)	1.9 (3)	0.4 (0.1, 0.9)*	2.4 (2)	0.3 (0.1, 1.0)
Bone/ Soft tissue	7.4 (31)	5.2 (8)	1.4 (0.4, 4.8)	4.8 (4)	0.4 (0.1, 2.2)
Skin	2.2 (9)	4.5 (7)	0.7 (0.4, 1.3)	2.4 (2)	0.4 (0.1, 0.7)*
Reproductive Concerns After Cancer Scale-Fertility potential domain (mean (SD))	3.5 (1.2)	2.6 (1.2)	0.7 (0.6, 0.8)*	3.7 (1.1)	1.2 (0.9, 1.5)
Ever Previous Infertility	17.7 (74)	4.5 (7)	0.2 (0.1, 0.5)*	16.9 (14)	0.9 (0.4, 1.8)

*p<0.05

[1] Following variables were not significant at p<0.05 in adjusted model: race, ethnicity, sexual orientation, relationship status, education, employment, household income, health insurance, general health, BMI, cardiovascular/pulmonary/other comorbidities, psychological comorbidities, stress, social support, years from cancer diagnosis, Reproductive Concerns After Cancer Scale - becoming pregnant domain, ever received fertility treatment

SUPPLEMENTAL INFORMATION I



Supplemental Figure S4.1. Decision tree on the categorization of objective infertility risk among study participants. **A:** participants reporting high-moderate and high gonadotoxic risk were categorized with impaired fertility **B:** Participants with low and both low-and moderate- moderate gonadotoxic treatments were categorized further by receipt of and type of hormonal therapy. **C:** Among participants receiving hormonal therapies (not including menopausal therapies) impaired fertility was determined by results of ovarian reserve testing (ORT). ORT included assessment of AMH and FSH, FSH was only included if a valid test was reported (i.e., participant was not pregnant at time of test). If no ORT was reported in this sub-group, participants were excluded because gonadal functioning could not be determined. **D:** Among participants not receiving any hormonal therapies, menstrual patterns were incorporated into fertility determination along with ORT results as applicable. Again, FSH was only evaluated if it represented a valid test.

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CHAPTER 5

DISCUSSION

DISCUSSION

Fertility and family planning are key areas of focus for AYA survivors.[1] Preconception health behaviors are a significant means to ensure healthy pregnancies and positive reproductive outcomes for both mother and child. No studies were identified that evaluated preconception health behaviors among female AYA cancer survivors and its association with pregnancy intention and perceived infertility risk. The current dissertation fills this important gap in knowledge on fertility optimization behavior and needs among a significant population.

Summary of Study Findings

Study #1: Association between pregnancy intention and preconception health behaviors to optimize pregnancy among female survivors of adolescent and young adult cancers

This study demonstrated that pregnancy intention was associated with some preconception health behaviors among female AYA survivors. Specifically, urgent pregnancy intention (*trying now)* was associated with more PA, while ambivalent intention was associated with lower alcohol consumption. This aligned with the proposed framework from the Rubicon Action Model in which urgent intention is likely associated with action because of a self-established deadline to achieve a goal. The construct of perceived susceptibility from the Health Belief Model (HBM) also was supported: AYA survivors with higher pregnancy intention and believed they were at risk of infertility engaged in more PA compared to women who did not perceive fertility loss. This study also established the utility of measuring ambivalent intention because although it represents an imprecise intention it is associated with alcohol use behavior. Although of note, this finding may require further substantiation through replicative studies. No associations were found with smoking behavior however it is noted in Chapter 2's Discussion section, smoking is a difficult behavior to change and our sample of current smokers was small

and may not have been powered enough to detect a difference compared to current non-smokers.

Study #2: The effect of changing pregnancy intentions on preconception health behaviors: a prospective cohort study

This study furthers our understanding of the relationship between pregnancy intention and preconception behaviors among female AYA survivors. Similar to Study #1, urgent dimension of pregnancy intention was associated with PA behavior. This study took into account changing pregnancy intentions during preconception and found increasing urgent intention measured by the *trying* dimension, was associated with more PA. Again this aligns with the proposed study framework. Perceived infertility risk did not effect modify the relationship between changing pregnancy intention and PA, but it did effect modify the relationship with smoking. Although there was no association between changing pregnancy intentions and current smoking behaviors, when stratified only participants who perceived infertility risk were more likely to smoke compared to survivors trying to become pregnant. However it is noted in Chapter 3 that results need replication because of the small sample size of both current smokers and those who did not perceive infertility risk.

Study #3: Perceptions and objective measures of infertility risk in female adolescent and young adult cancer survivors

To date, this study was the first to characterize factors associated with fertility perceptions and to contextualize the agreement between perception and objective infertility risk among female AYA survivors. This study found both higher gonadotoxicity of cancer treatment and amenorrhea were associated with higher odds of infertility risk perception. Additionally, survivors perceived risk was in poor agreement with objective infertility risks.

Recommended Future Research/ Clinical Implications

Some potential areas to target with intervention research identified by this dissertation project are preconception education tailored on pregnancy intention, emphasis of fertility concerns and long-term fertility surveillance by specialists within survivorship care plans. The following recommended future research are informed by this dissertation as well as current literature in the field of preconception health and survivorship care.

Chapter 2 & 3 demonstrated urgent pregnancy intention measured by the *trying* dimension was associated with preconception PA. Future studies could assess these associations in a behavioral intervention that tests the outcomes of a preconception health education toolkit for female AYA survivors visiting survivor clinics. This intervention could evaluate if targeted education based on urgency of intention is associated with higher prospective PA. Findings from Chapter 4 support the incorporation of infertility risk education within preconception PA behavior interventions. As an effect modifier, perceived infertility risk would impact subsequent PA and as Chapter 4 found, survivors do not have an accurate perception on their risk. Clinically, providers caring for AYA survivors may screen for pregnancy intention to guide education and conversations on preconception behaviors even among women reporting ambivalent intention. Incorporation of urgent pregnancy intention screening in survivorship care can help facilitate early preconception health promotion and education.

Additional clinical implications of this dissertation include the need for incorporating repeated fertility counseling and assessments for survivors to reduce psychological distress and bridge the gap between perception and objective infertility risk. This dissertation specifically identified female AYA survivors who experience higher gonadotoxic treatment and/or experience amenorrhea, are in need of repeated fertility education and support. Survivors readily report gaps in information[2,3], which may lead to discordance found in Chapter 4. As suggested in Chapter 4 these gaps can be improved with greater emphasis on fertility concerns and strategies post-cancer treatment within survivorship care plans. Past studies with AYA

survivors show the use of survivorship care plans can improve infertility concerns and reduce unmet information needs.[4,5] Most guidelines on care for AYA survivors focus primarily on fertility preservation and conversations before treatment, which is limited by access disparities based on race/ ethnicity and socioeconomic status. Future studies may assess the association between repeated access to survivorship clinics, visits with an endocrinologist, and or receipt of fertility counseling post-treatment on accuracy of infertility risk perception. Overall, improved communication between survivors and their physicians/ care teams through tailored communication, survivorship plans, and consistent surveillance of objective fertility can improve quality of life and family planning for AYA survivors.

These series of studies are novel within the female AYA cancer population. As evidenced in each chapter some associations did not align with research done in either general populations of women or childhood cancer survivors. For example ambivalent intention was associated with reduced alcohol consumption in Chapter 2 where as studies in general population of women have found no association and one study found ambivalent intention was associated with increased smoking behavior [6] Additionally, irregular periods were not associated with perceived infertility risk in Chapter 4 where as most research indicates irregular periods are associated with increase concern of infertility and or overall health.[7–10] Sample bias may have affected these results as women consenting to be part of the original Window study may have differed from female survivors who did not elect to participate in a study on reproductive potential post cancer treatment. Future replicative studies may elucidate the strength of these relationships among female AYA survivors.

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