PREGNANCY AND MULTIPLE SCLEROSIS: RISK OF UNPLANNED PREGNANCY, DRUG EXPOSURE IN UTERO, RELAPSE WHILE ATTEMPTING CONCEPTION, AND POST-PARTUM RELAPSE BY ANESTHESIA CHOICE

BY

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Submitted in partial fulfillment of the requirements

For the Degree of Master of Science

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Clinical Research Scholars Program

CASE WESTERN RESERVE UNIVERSITY

August 2017

CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF GRADUATE STUDIES

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Abbreviation List

95% CI	95% Confidence Interval
AIC	Akaike information criterion
AMH	Anti-Müllerian hormone
ANOVA	Analysis of Variance
ARR	Annualized Relapse Rate
BMI	Body Mass Index
C-section	Caesarian Section
CI	Confidence Interval
DMT	Disease Modifying Therapy
EDMUS	European Database for Multiple Sclerosis
EDSS	Expanded Disability Status Scale
EMR	Electronic Medical Record
FSS	Functional Systems Scores
IRB	Institutional Review Board
LMP	Last Menstrual Period
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NARCOMS	North American Research Council on Multiple Sclerosis
PRIMS	Pregnancy and Multiple Sclerosis Study
RR	Relapsing Remitting
RRMS	Relapsing Remitting Multiple Sclerosis

Pregnancy and Multiple Sclerosis: Risk of Unplanned Pregnancy, Drug Exposure In Utero, Relapse while Attempting Conception, and Post-Partum Relapse by Anesthesia Choice

By

ANDREW SMITH, MD

Abstract

Background: Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system that commonly affects young women of reproductive potential. As such, issues related to family planning are of critical importance.

Objective: The objective of this study was to first determine both what are the risk factors of having an unplanned pregnancy and the risk factors of having a relapse while attempting to conceive. Secondly, we look at the rate of post-partum relapses as a function of labor anesthesia choice.

Methods: A retrospective observational cohort study was created from a chart review. Multiple stepwise logistic regressions were used to determine the risk factors for a relapse while attempting, unplanned pregnancies, and DMT exposed pregnancies. Cox modeling was used to predict post-partum relapse

Results: 150 patients were identified as having MS and concomitant pregnancy. The medical records of these patients were reviewed and 45 patients had both obstetric and MS care within the Cleveland Clinic hospital system. There were a total of 63 pregnancies (20 unplanned and 43 planned). Risk factors for unplanned pregnancy were younger age ($p < 0.01$), being on DMT ($p < 0.001$), and being unmarried ($p < 0.001$). Among those with planned pregnancies, the risk of relapse was dependent only on the time it took to conceive ($p < 0.001$). Of the total 63 deliveries, there were no significant differences in the number of post-partum relapses or time to relapse among the different anesthesia modality groups ($p = 0.71$).

Conclusion: The rate of unplanned pregnancies is lower than previous though. Intervention at younger unmarried patient may lead to reduce rate of unplanned and DMT exposed pregnancies. MS patients should be referred to reproductive medicine sooner to avoid return of disease activity. Finally, MS should not affect anesthesia used during delivery.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disease of the central nervous system that leads to progressive permanent disability in most patients. There are approximately 400,000 people in the United States diagnosed with MS (1), and the prevalence is increasing (2). This increasing prevalence appears to be due to an increase mainly in relapsing remitting (RR) phenotype mostly in women over the course of the 20th century (2-4). Fortunately, the RR phenotype of MS is highly treatable, with 15 different disease-modifying treatments (DMT) that reduce relapse rate and potentially prevent or delay permanent neurologic disability (5, 6). Evidence suggests early initiation of effective DMT leads to better outcomes in RRMS patient (7-9). However, given that the disease affects women of reproductive potential, the need for early treatment needs to be balanced with a patient's reproductive plans. While the Pregnancy in MS (PRIMS) study addressed several questions about pregnancy in MS, many questions remain such as the risk factors and rate of unplanned pregnancy in the MS population, the risk of relapse while attempting conception, and whether the post-partum relapse risk depends on anesthesia used during labor and delivery. Over the follow paragraphs existing literature will be reviewed.

Rate of unplanned pregnancy

Currently, no data exist exploring the rate of unplanned pregnancy in MS patients. Estimates suggest that as many as 50% of pregnancies in the general population in the United States are unplanned (10). If the unplanned pregnancy rates in the United States

hold true for the MS population, then high concerns exist. Currently DMT and most symptomatic treatments used in MS are not considered completely safe in women who are attempting to conceive, pregnant, or nursing. Because unintended in utero exposure of medication used in the treatment of MS can potentially lead to teratogenic effects, long term disability, and intellectual impairment in the offspring, it is critical that women are adequately counseled about family planning issues (11, 12). Studies show that family planning issues are brought up by only 57% of physicians when starting a DMT in women of child bearing potential (13). While clinic time is limited, methods to assure that women are adequately counseled on risk are needed. Moreover, determining the optimal intervention to address these issues will require accurate measurements of the unplanned pregnancy rate and identification of the at risk population.

While little evidence exploring unplanned pregnancies in the MS population exists, data has been generated in the teenage and military populations. From these groups, women who were younger than 30, unmarried, attained lower educational levels, economically disadvantaged, depressed, non-Caucasian, and used birth control incorrectly were more likely to have an unplanned pregnancy (14-17). Due to perceived stress, psychosocial problems, and lack of adequate prenatal care, these women were more likely to have preterm deliveries and infants with low birth rates (14). Moreover, infants that were products of unplanned pregnancies were more likely to suffer childhood growth stunting, poor child development, and subsequent child abuse or neglect. Additionally, women with unplanned pregnancies were more likely to have obstetric complications and infections (18). Therefore, reducing unplanned pregnancies

in all women and not just MS patients could lead to improved outcomes for Mother and baby and possibly less health care costs.

Multiple approaches exist to reduce the risk of unplanned pregnancies, which, thus, should be preventable. As many as 40% of unintended pregnancies are due to women using their contraceptive method inconsistently or incorrectly (16). By simply providing family planning education to women of child bearing age, the rate of contraceptive usage increased with a corresponding drop in the rate of unplanned pregnancies (15). Other suggested methods of reducing contraceptive failure include utilization of less error prone forms of birth control like oral birth control, intra uterine devices, and injectable hormonal therapy (16). While implementing full family planning education is outside of the expertise of most neurologists, making simple inquiries about the use of birth control and recommending follow up with the patient's gynecologist or primary physician can be implemented rather easily into the clinical visit.

Planning to conceive

Women desiring children are frequently faced with a difficult choice after diagnosis of MS. Patients with evidence of active demyelination are encouraged to start DMT, except in the case of women who knowingly want to become pregnant (19). A common approach that is based on limited data has a patients go on a DMT for 1-2 of years to control underlying disease activity. The idea of controlling the disease activity prior to pregnancy comes from the PRIMS study, which showed that pre-pregnancy rate

predicted the post-partum relapse rate (20). Some studies suggest that patients who achieve lower relapse rate prior to pregnancy due to DMT, have a lower post-partum rate (19).

While MS disease activity tends to decrease during pregnancy, anxiety exists for the period of time women of childbearing potential go off of DMT until they become pregnant (21). Studies suggest that it takes an MS patient approximately 7 months to become pregnant (22). With return of disease activity that typically occurs a few months after discontinuing DMTs, the risk of relapse discourages some from even planning conception (23), Therefore, predictors of relapse during the time attempting to conceive would be helpful when counseling patients.

While on a population level, fertility is not affected in MS patients, conception is delayed in some women. Several studies suggest signs of lower ovarian reserve measured by anti-Müllerian hormone (AMH) in patients with MS (23). Additionally, those with the most active disease, which would be the patients that would be most encouraged to start DMT, had the lowest AMH levels (24). Therefore, by asking the most active patient to delay pregnancy until their disease is under control might lead to lower success of pregnancy due to natural lowering of AMH with age (25). This issue further highlights the need for better data concerning the risk of relapse while attempting to conceive and for strategies to help ameliorate this problem.

Delivery Anesthesia choice in MS

During labor and delivery in the United States, many women use epidural anesthesia for vaginal delivery and spinal anesthesia for Caesarian section (C-section) delivery to help with the pain of child birth. The use of epidural anesthesia and spinal anesthesia in MS patients was controversial in the past. Several older case reports in anesthesia literature suggested increased disease activity and progression in MS patients who had received anesthesia for labor and delivery. This observation led to a recommendation against the use epidural and spinal anesthesia in MS patients.

The first large study that suggested epidural anesthesia was not harmful was PRIMS, which demonstrated no increased rate in post-partum relapse in women receiving epidural anesthesia (20). After this study, several studies corroborated the safety of epidural anesthesia in MS patients (26, 27). Moreover, case studies in the early 2000s, suggested that spinal anesthesia is safe (26). In 2013 a large Italian cohort was published, consisting of over 400 pregnancies with 155 who underwent C-section (presumably with spinal anesthesia) and 65 receiving epidural anesthesia. There was no difference in post-partum relapse rate between spinal anesthesia and no anesthesia or between epidural anesthesia and no anesthesia (28). The current study will attempt to confirm these findings in an American cohort, including a comparison of post-partum relapse rate following spinal anesthesia and epidural anesthesia.

Thesis Aims

This thesis will cover three topics. First, this study will determine the rate of unplanned pregnancy in MS patients. Second, in patients with planned pregnancy(ies), this study will determine the risk of relapse and risk factors for relapse while attempting to conceive. Finally, this study will assess the effect of anesthesia choice during delivery on post-partum disease activity.

Methods

Patient identification

The study population consisted of patients who received medical care within the Cleveland Clinic care system in Cleveland, Ohio. The Mellen Center is a large MS specialty clinic, which sees over 20,000 patient visits per year. From this population, an automated electronic medical record (EMR) data pull identified 181 pregnancies in 150 patients with ICD10 codes for pregnancy and MS from 2000 to 2016. The EMR of these 150 patients underwent a comprehensive review of their entire chart including all office visits, telephone calls, and direct patient provider EMR messaging encounters. This data was extracted by a single reviewer (AS) in order to create a retrospective database. Patients were then excluded from analysis if they did not have MS, if pregnancy was prior to being diagnosed with MS, if they did not deliver within the Cleveland Clinic network, or if they did not have neurologic follow up at the Mellen Center. After applying these exclusion criteria, 64 pregnancies in 43 women were included in the final analysis (Figure 1).

Measurements of Outcomes of Interest

The thesis addresses each of the three aims independently and is divided into subsections to address each of three aims. The first aim attempts to determine the proportion of and risk for unplanned pregnancies. The second aim of the thesis analyzes the risk for relapse during the time attempting to conceive in those who planned to become pregnant. The third aim determines the time to post-partum relapse as a function of type of anesthesia used during labor and delivery.

A pregnancy was defined as unplanned if it was specifically documented that the pregnancy was unplanned in the first obstetrics note. If this criterion was not met, then information in the rest of the chart was considered. Specifically, the reviewer looked for evidence that the patient required instruction on starting prenatal vitamins or folic acid or asking the doctor what the patient needs to do after the discovery of the pregnancy. Additionally, the chart was reviewed for absence of evidence that pregnancy was planned. If both of those criteria were met, then the pregnancy was considered unplanned. Otherwise the pregnancy was considered planned. A secondary outcome measure for the first section was being on DMT while pregnant.

Regarding whether the patient had a relapse while trying to conceive, for the purpose of this study, an event was considered a relapse if one of two criteria were met: if the event was specifically called a relapse by a neurologist or if a narrative from a patient encounter described new or increased neurologic symptoms lasting longer than

24 hours without evidence of infection which was more than one month after recovering from a previous relapse. The time period when the patient was trying to conceive was defined as the time from when the patient stated she was trying to become pregnant until her last menstrual period (LMP) prior to becoming pregnant. LMP was chosen because it is commonly used as a surrogate for conception date due to uncertainty surrounding the precise date of conception and relative certainty of the LMP date. If the patient did not give an exact date when she was trying to become pregnant, it was assumed that she started on the 15th day of the month she stated she was going to try to become pregnant. If there was no evidence of a time when the patient was trying to become pregnant, but the pregnancy was documented as planned, the time trying to become pregnant was set to 15 days. In addition to determining who had a relapse, a secondary outcome looking at the number of relapses in the time period trying to conceive was also conducted.

For the final aim, the outcome of interest was time from delivery to first clinical relapse, assessed by survival analysis. If the patient did have a relapse documented after delivery, they were censored at the time of their last clinical visit prior to 12/31/2016. For this part of the study, secondary outcomes included number of new T2 and enhancing lesions on the first post-partum MRI (extracted from the radiologist report), number of relapses in the year post-partum, first post-partum EDSS, change in the post-partum EDSS compared to the pre-pregnancy EDSS, and change in post-partum timed 25-foot walk compared to the pre-pregnancy timed walk. If the note did not contain an EDSS, it was estimated based on documented examination and narrative of the note. If

the note or patient's exam did not comment on a Functional System Score component of the EDSS, it was assumed to be normal or unchanged from that documented in the previous note.

Measurement of exposures of interest

The exposures of interest consequently relate to the three outcomes listed above in each section. In the first section, the exposures of interest were whether the patient received documented family planning counseling. In the second section, the exposures of interest were the duration of time trying to conceive, the number of relapses in the year prior to trying to conceive, whether the patient discontinued DMT prior to attempting to conceive, and the intensity of the DMT. DMT intensity was a tri-level factor variable: no therapy, injectable therapy, or oral or infusion therapy. Finally, for the third section, the exposure of interest was anesthesia choice, which was a three-level nominal variable consisting of epidural anesthesia, spinal anesthesia, or no anesthesia. The information about anesthesia used was extracted from the delivery note, obstetrician's note, anesthesia notes, and the medicine administrative record.

Covariates of interest

Several covariates were extracted from the patient's EMR to determine their effects on outcome of interests for the purposes of modeling. For each section, the following

covariates were collected and analyzed: demographic factors (age, race, marital status), obstetric history (pregnancy outcome, infant delivery weight, infant Apgar scores, previous pregnancies, previous pregnancy outcomes, complication with delivery, need for C-section, breast feeding choice, and breast feeding duration), clinical and MS information (age of diagnosis of MS, age at delivery, smoking status, last measured pre-pregnancy basal metabolic index [BMI], use of DMT during pregnancy, use of birth control, time to restarting DMT post pregnancy, number of relapses the year before pregnancy, number of relapses during the pregnancy, number of new T2 and enhancing lesions on MRI prior to becoming pregnant). Additionally, outcomes and exposures from other sections were included as covariates for other sections.

Statistical Analysis

AIM 1: Determining risk factors for planned versus unplanned pregnancy.

Data were de-identified by removing all health protected information. Characteristics of patients who had planned versus unplanned pregnancies were compared using Chi-square and t-tests for categorical and continuous variables. Next, a logistic regression model was constructed to determine the effect of family planning counseling on the log odds of whether a pregnancy was planned or unplanned. Then a Spearman plot with all the collected covariates was constructed, from which a model was created with the variables that had the highest Spearman correlation coefficients. From that model a bidirectional stepwise logistic regression was performed to generate a model with

lowest Akaike information criterion (AIC) value. Subsequently, the p-values of the Logit was calculated using the t-test and Chi-squared test depending on the variable type. The Logit was used to calculate the odds ratio and 95% confidence intervals (CI) that each model component had on the likelihood of unplanned pregnancy.

Secondary goals of this aim were to explore the proportion of DMT exposed pregnancies in this cohort. A Chi-squared test was done to analyze the relationship between planned and unplanned pregnancy. Next a logistic regression analysis comparing pregnancy outcomes in planned versus unplanned pregnancies and DMT exposed and non-DMT exposed pregnancies was undertaken.

AIM 2: Predictors of relapse while attempting conception

A filter was applied to the main database to remove all patients who had an unplanned pregnancy. Among the remaining pregnancies, characteristics of patients who did and did not relapse while attempting conception were compared using Chi-square and t-tests for categorical and continuous variables. A logistic regression model was generated to determine the effect that discontinuing DMT prior to attempting to conceive, the duration that it took to conceive, and the number of relapses in the year prior to attempting to conceive would have on the log odds of whether a patient relapsed or not while attempting to conceive. After calculating the odds ratio for each component, a Spearman plot with all collected covariates was used to construct a model with variables with the highest spearman correlation coefficients. From that model a bidirectional

stepwise logistic regression was performed to generate a model with lowest AIC value. The p-value of the Logit was calculated using the t-test and Chi-squared test depending on the variable type. The logit was used to calculate the odds ratio and 95% CI that each model component had on the likelihood of whether or not a patient relapsed while attempting to conceive.

AIM 3: Predicting post-partum relapse based on labor and delivery anesthesia

For this part, all pregnancies with information on the delivery and post-partum neurologic follow up where included. Characteristics of patients who either received no, epidural, or spinal anesthesia were compared using analysis of variance (ANOVA). First, a simple Cox model was utilized for the time to event variable of time to post-partum relapse among anesthesia group. Comparison among groups was conducted using log rank tests for time to event. Linear models were constructed comparing average number of relapses in the post-partum year, changes in EDSS, and new T2 or enhancing lesions on the first post-partum MRI. ANOVA was used to make statistical comparisons among the variables composing the linear models.

Adjustment for multiple comparisons

For each aim, statistical significance was defined as $p < 0.05$ with Bonferroni correction made for multiple for multiple comparisons. After correcting by a factor of 20, statistical significance was defined as a p value less than 0.0025

Results

Unplanned pregnancy rate and risk factors

Baseline characteristics are summarized in table 1. Comparing patients with unplanned pregnancies to those with planned pregnancies, patients with unplanned pregnancies were younger than 30 at delivery (11 (55%) versus 7 (17%), $p = 0.004$, figure 2), were unmarried (12 (60%) versus 42 (98%), $p < 0.001$, figure 3), were on DMT at the time of conception (13 (65%) versus 4 (9%), $p < 0.001$), and were reportedly on birth control (5 (25%) versus 0 (0%), $p < 0.001$). Additionally, the proportion of those receiving family planning counseling was also lower in the patients with unplanned pregnancies (10 (50%) versus 41 (95%), $p <0.001$, figure 4). Of those who received family planning counseling, women with unplanned pregnancies were less likely to initiate the conversation about reproductive goals than those who had planned pregnancies (4 (40%) versus 38 (93%) $p < 0.001$). Women with unplanned pregnancies compared to those with planned pregnancies also were less likely to breastfeed (7 (35%) versus 27 (63%), $p = 0.04$) and were less likely to have an enhancing lesion on their first post-partum MRI (3 (15%) versus 22 (47%), $p=0.015$). No other differences reached statistical significance.

Starting with the simplest logistic regression models, those who did not receive family planning counseling had a substantially greater likelihood of having an unplanned

pregnancy than those who received counseling (OR = 20, 95% CI 4.5 to 148, $p < 0.0001$). The R^2 from this model was 0.339 ($p < 0.001$)

For the more complex model, the 5 covariates with the highest Spearmen correlation coefficients where chosen for the next model. The remaining variables after the bidirectional stepwise logistic regression consisted of pregnancy number of the current pregnancy, counseling, marital status, and age greater $\geq$30 at the time of delivery. The odds ratios with 95% CI from the regression model can be seen in table 3 and figure 5. In final models, those who did not receive family planning counseling had 0.028 times the odds of having a planned pregnancy than those who received counseling ($p < 0.0011$, figure 5). Patients who were married at their first prenatal visit had 17.4 times the odds of having a planned pregnancy than those who were not married ($p=0.06$). Those who entered their 4^{th} decade had 13.9 times the odds of having a planned pregnancy compared to those who were younger ($p<0.01$). Finally, patients who were pregnant for the first time had 0.2 times the odds of having a planned pregnancy compared to their multigravida counterparts ($p=0.07$). The model left after the stepwise logistic regression better predicted the risk of unplanned pregnancy with an R^2 of 0.634. Regardless of model chosen, counseling patients decreases the risk of having an unplanned pregnancy.

When examining the secondary outcome of being on DMT at pregnancy onset, those whose pregnancies were unplanned were 25 times (95% CI 6.25, 131) more likely to be on DMT while pregnant than those whose pregnancies where planned ($p < 0.0001$). Additionally, only 4 of 16 patients who became pregnant while on DMT were

on birth control. When examining the birth outcomes of unplanned versus planned pregnancy status, there were no statistically significant differences in gestational age at delivery ($p = 0.63$), birth weight ($p = 0.75$), Apgar score at one minute ($p = 0.83$), Apgar score at five minutes ($p = 0.267$), proportion of birth defects ($p = 0.99$), proportion of infants transferred to the neonatal intensive care unit ($p = 0.42$) and the proportion of C-sections ($p = 0.65$). Finally, when examining the birth outcomes of comparing DMT exposed versus non-DMT exposed pregnancies, there were no statistically significant differences in gestational age at delivery ($p = 0.23$), birth weight ($p = 0.69$), Apgar score at one minute ($p = 0.12$), Apgar score at five minutes ($p = 0.17$), proportion of birth defects ($p = 0.99$), proportion of infants transferred to the neonatal intensive care unit ($p = 0.57$), and the proportion of C-section ($p = 0.31$)

Determinants of relapse while attempting to conceive

Baseline characteristics of the population are summarized in table 4. As a group, patients experiencing a relapse while trying to conceive were of a different racial make-up than those who did not have a relapse ($p = 0.041$). However, given the low number of non-Caucasians in this subset, this difference should be interpreted with caution. No other covariates reached statistical significance. Table 4 examines the potential predictors of having a relapse while attempting to get pregnant. The only statistically significant difference between those who relapsed and those that did not, was the duration of time needed to conceive (110 days versus 321 days, $p < 0.001$). Neither the

proportion of patient's who discontinued DMT among (23 (72%) versus 6 (55%), p = 0.301) nor the ARR the year prior to attempting to conceive (0.38 versus 0.64, p = 3.14) differed between those who did or did not relapse.

Starting with the simplest logistic regression models, those who discontinued DMT had 0.47 times (95% CI 0.11, 1.93) the odds of having a relapse than those who did not. For each relapse that a patient had the year prior to trying to get pregnant, the odds of having a relapse increased by 1.57 (95% CI 0.65, 3.81) times. Finally, for each standard deviation above the mean time attempting to conceive, the odds of having a relapse increased by 3.27 (95% CI 1.34, 7.95). The R^2 for this model was 0.324. The odds ratio with 95% CI from the regression model can be seen in table 5. The odds ratio for time trying to conceive, ARR in year prior to attempting to conceive, pre-pregnancy BMI, and number of new T2 lesions on the pre-pregnancy MRI were 3.8 (p = 0.007), 2.69 (p = 0.15), 1.91 (p = 0.17) and 0.13 (p = 0.064), respectively. The R^2 of this model was 0.468.

Time to post-partum relapse by anesthesia choice during labor

Baseline characteristics of the population are summarized in table 7. Except for the proportion of patients delivering by C-section, there were no statistically significant differences among the groups. In addition, there were no differences in outcomes of interest among the anesthesia groups by simple ANOVA analysis (table 7). Average time to relapse for the anesthesia groups were 643 days for epidural anesthesia, 638 days for no anesthesia, and 551 days for spinal anesthesia (p = 0.93). Log rank survival analysis

comparing the survival curves did not demonstrate a difference among anesthesia use ($p = 0.718$, figure 9). ARR in the year after pregnancy was 0.68 in the epidural anesthesia group, 0.54 in the no anesthesia group and 0.58 in the spinal anesthesia ($p = 0.84$, figure 10). Of those who had MRIs, the average number of post-partum enhancing lesions was 0.89 in the epidural anesthesia group, 0.62 in the no anesthesia group, and 1.00 in the spinal anesthesia group ($p = 0.78$, figure 11). The number of T2 lesions on the post-partum MRI were 1.65 in the epidural anesthesia group, 2.15 in the no anesthesia group, and 1.83 in the spinal anesthesia group ($p = 0.674$, figure 12). Finally, change in EDSS score compairing pre-pregnancy to post-partum EDSS was 0.26 in the epidural anesthesia group, 0.15 in the no anesthesia group, and 0.25 in the spinal anesthesia group ($p = 0.930$, figure 13).

Linear regression models were used to determine if any of the other variables were associated with the outcomes of interest. Only the number of relapses in the year prior to pregnancy predicted the number of relapses post-partum ($p < 0.004$). The number of new T2 lesions on the post-partum MRI was significantly associated with BMI prior to pregnancy ($p < 0.008$), number of relapses the year prior to pregnancy ($p < 0.001$), number of enhancing lesions on the post-partum MRI ($p < 0.00001$), and number of enhancing lesions on the prior MRI to pregnancy ($p < 0.006$). The number of enhancing lesions on the post-partum MRI was stastistically associated with being on DMT prior to pregnancy ($p = 0.03$), number of relapses in the year prior to pregnacy ($p = 0.019$), the number of new or enlarging T2 lesions on the post-partum MRI ($p < 0.000001$), and number of enhancing lesions on the MRI prior to pregnancy ($p = 0.0047$).

Finally, the change in EDSS from pre-pregnancy to post-partum was predicted only by the patient's pre-pregnancy EDSS and post-pregnant EDSS ($p < 0.00001$).

Discussion

MS is a disease that disproportionally affects woman of reproductive potential. Therefore, research looking into reproductive health is a critical but sometimes forgotten aspect of clincal research and practice in medicine in general (29). The goal of present study was to add to existing data in the field of pregancy, post partum relapse rates in MS and the importance of family planning education for MS patients.

These results suggest that women who are counseled prior to becoming pregnant after a MS diagnosis are substantially more likely to plan their pregnancy than those without counseling. The overall proportion of unplanned pregnancy in this cohort was 32%. Prior to this study, the number the unplanned pregnancies was assumed to be 50% (30), based on the national average. Given the make up of this cohort, the age corrected unplanned pregnancy rate should be 28.2% (31). Other known risk factors for unplanned pregnancy, e.g. age, race, martial status, and whether there was a prior pregnancy, were included in the model. Still, the importance of counseling patients remained. However, half of those with unplanned pregnancies were counseled. This observation suggests that either counseling alone is not effective, or that effective counseling needs to be discussed multiple times with the patient instead of mainly just at diagnosis and onsent of a new DMT. In this sample, most of those with unplanned

pregnancies who were counseled, only had family planning counseling documented once in the chart. Therefore, a possible intervention to address infrequent family planning counseling would be to include brief review of reproductive goals during all clinical follow up visits.

Another important result is the low proportion of birth control use among women on DMT who became pregnant; only a quarter of the patients were on DMT when they became pregnant. Of those who were on DMT when they became pregnant, 81% of those pregnancies were unplanned. Only 4 of 16 women who had DMT exposure during pregnancy were documented as being on any form of birth control. This number probably underestimates the true birth control usage rate in the unplanned pregnancy group due to not counting the use of barrier methods. Therefore, this observation highlights the importance of not only discussing family planning and use of birth control when on DMT but also ensuring that patients are using birth control correctly. While neurologists may not be familiar with all of the options for birth control and their correct use, they can either encourage the patient to discuss the options with their gynecologist or primary care physician or make an appropriate referral. With most clinics implementing EMRs in regular practice, ensuring adequate birth control use while on DMT could be automated. For example, an automated alert could be triggered within the EMR when patients starts or is on DMT or other teratogenic medication to remind the provider about family planning counseling.

Factors like the number of relapses the year prior to planning on getting pregnant and whether or not patients discontinued DMT did not significantly increase

the risk of relapse while attempting conception. The final model did not include DMT discontinuation as a variable of risk for relapses during conception. Only the amount of time attempting to conceive predicted risk of relpase, which suggests that methods should be implemented to reduce the time women are attempting to conceive. While fecundity and fertility are not classically affected in MS (22), there is evidence suggesting that MS women have decreased reproductive reserve (23). With up to 20% of women having difficulties getting pregnant, consideration could be given to an early referral to a reproductive specialist (19).

While discontinuing a DMT was not found to be a risk factor for relapse while attempting to get pregnant, this result should be interpreted with caution. Fewer than 20% of patients were on moderate to high efficacious drugs prior to planning to become pregnant. Therefore, the sample may not have been large enough to detect the return of previously controlled disease activity or even rebound phenomena that is seen when discontinuing higher efficacy DMT (32). Therefore, due to the concern for the return of disease activity , some neurologists recommend that their patient continue on a safer DMT while attempting to conceive. In those who had been on oral birth control for prolonged periods of time, it can take 5-6 months until ovulation resumes. Consequently, neurologists can continue the patient on their current DMT while using barrier methods, until fertility can be confirmed by blood work.

These results demonstrated that the type of anesthesia used at delivery does not affect the short term course of MS. While multiple factors determine the type of anesthesia used in delivery, this knowledge should allow the selection of anesthesia to

be based upon medical necessity and patient preference. These data further suggest that patients who receive spinal and epidural anesthesia are no more likely to have post partum MS disease activity than those who do not use anesthesia during the delivery. Moreover, this study confirms previous studies indicating that post partum MS disease activity is largely dependent on the prepregnancy disease activity, which has been documented multiple times since the PRIMS study (20).

Several major limitations exist in these analyses. The first and most critical limitation is the fact that this was a retrospective chart review. The analyses depended on the data that was available in the chart, which might be incomplete or inaccurate, thus leading to misclassification bias. For example, the major variable of whether a patient was counseled was dependent on what was documented in the chart. Evidence exists to suggest that preventive counseling rates may be underreported in the medical chart compared to observed during a clinical encounter. Studies suggest that the mismatch between what actually happened during the patient exam and what is documented may be as high as 30% (33-35). Besides potentially underestimating the rate of clinical provider counseling at the visit, the difference in patient initiated reproductive goal discussion may have led to a recording bias in charting family planning counseling among those actively planning to conceive. Another issue is that although this was an extensive chart review, it only included the records at the Cleveland Clinic. It was impossible to measure any family planning counseling that the patient may have received from outside sources such as the pharmaceutical company, pharmicist or other provider. Almost all patient information of MS DMT contains information warning

women against becoming pregnant and exhorts women to use reliable forms of birth control. Besides the concerns of using chart extraction to measure the rate of preventitive counseling done in the clinic, some data were impossible to extract from the chart review. For example, given that this study relied on ICD 9 and 10 codes for pregnancy, this study only captures the time trying to conceive in those who became pregnant. This analysis completely missed those who tried to become pregnant and failed. Ideally, these issues could be better addressed by following a prospective cohort, which would allow data to be collected in a more systematic fashion. Furthermore, it would allow for increased recruitment due to patients not being required to receive all of their care within one medical system.

Another limitation is that the cohort was small and from a single center. First, the practice of discontinuing all DMT when a woman attempts to conceive is not a universal practice. Therefore, this data may be of questionable use in centers that continue DMT in those planning to conceive. Another concern would be that the study may have been underpowered to detect an effect for some of the exposures of interest due to its small size. However, in spite of the small size, the study did detect and confirm many known risk factors for post-partum relapse and unplanned pregnacies. A final issue is that the study population that comes to a quanternary center may differ from the general MS clinic. Therefore, these results may suffer from selection bias, due to our patients having potentially more aggressive disease, limiting generalizability.

To circumvent the problems of the study being small and conducted in a single center, the next logical step would be to validate the results in a broader clinical setting.

Ultimately, a prospective multicenter study would be optimal. Ideally this can be accomplished by establishing a new pre-pregnancy registry or partnering with an existing research collaborative to start collecting these data to better answer these questions. Many national and international registries like European Database for Multiple Sclerosis, Accelerated Cure Project, North American Research Commity on Multiple Sclerosis, and MSBase currently exist. Additionally, pharmacuetical companies collect information about DMT exposed pregnancies as part of post-marketing research. Utilizing existing data already collected by these databases, could be the easiest method of validating the research in this thesis. However, the likelihood that data were collected at all let alone in a similar fashion in these databases is low. The risk would be that the data may not be comparable and may not answer the underlying questions put fowarded by this thesis. Another benefit of utilizing existing networks would be the potential networking connections that could be made. Meeting collaborators who would be interested in potentially validating the results of this study in a different clinical setting, would be the next step. Development of a network of individuals interested in this subject followed by the building of a large registry of reproductive health in MS would be desirable. The funding of such a project would probably need to come from government sources, not-for-profits like the National Multiple Sclerosis Society, or industry sponsors.

Conclusions

This study demonstrated that the risk of unplanned pregnancy in patients with MS is greatly impacted by whether the patient received family planning counseling. Moreover, data confirmed that factors like age, martial status, and having a prior pregnancy, also predicted the risk of unplanned pregnancy in MS as it does in other settings. To my knowledge, this study is the first to determine the rate of unplanned pregnancy in a MS cohort. Another concerning issue is that unplanned pregnancy was also highly associated with DMT exposed pregnancies. The time it took to become pregnant greatly affected whether a relapse and number of relapses happened while trying to conceive. Suprisingly, discontinuing DMT and the number of relapses in the year prior to trying to conceive were not associated with relapse. In contrast, attempted pregnancy did predict relapses post-partum. Finally, this study confirmed that type of anesthesia used during delivery does not effect the likelihood of post partum relapse in a United States cohort. While this study was limited by it small numbers and retrospective design, it has been able to address several issues previously largely unexplored in the field.

Tables

Table 1: Baseline demographics comparing unplanned versus planned pregnancies

	Unplanned	Planned	p-value
N	20	43	
Married (%)	12 (60)	42 (98)	<0.001
Pre-pregnancy BMI (mean (sd))	26.74 (9.12)	25.80 (5.83)	0.63
Age at MS diagnosis (mean (sd))	25.32 (4.96)	27.41 (5.07)	0.13
Age at delivery (mean (sd))	29.48 (5.55)	33.04 (4.33)	0.007
Relapse in the pre-pregnancy year (%)	6 (30)	17 (40)	0.472
Average ARR pre-pregnancy year (mean (sd))	0.55 (0.83)	0.63 (0.98)	0.759
Relapse after pregnancy (%)	18 (90)	31 (71)	0.115
Relapse within the first post-partum year (%))	12 (60)	21 (49)	0.417
Average ARR post-partum year (mean (sd))	0.60 (0.68)	0.65 (0.90)	0.822
Duration of maternal MS at delivery (mean (sd))	4.16 (3.53)	5.63 (3.64)	0.139
On DMT during pregnancy (%)	13 (65)	9 (07)	<0.001
C-section (%)	5 (25)	19 (44)	0.149
Birth weight (mean (sd))	3.31 (0.51)	3.13 (0.55)	0.244
Gestational age (mean (sd))	38.75 (1.21)	38.52 (1.69)	0.59
Age of menarche (mean (sd))	12.78 (1.64)	12.04 (1.24)	0.17
Gravida (mean (sd))	1.95 (1.15)	1.77 (1.07)	0.539
Breast feed (%)	7 (35)	27 (63)	0.04
Duration of breast feeding in days (mean (sd))	44 (87)	100 (128)	0.079
Time to restart DMT in days (mean (sd))	392 (684)	389 (525)	0.984
Smoking (%)	6 (30)	5 (12)	0.076
Race (%)			0.792
Black	1 (5.0)	4 (9.3)	
Hispanic	1 (5.0)	3 (7.0)	
White	18 (90.0)	36 (83.7)	
EDSS pre-pregnancy (median [IQR])	2.25 [1.00, 2.50]	2 [0.50, 2.50]	0.319
Post-partum EDSS (median [IQR])	2 [1.38, 3.00]	2 [1.50, 2.50]	0.712
Change in EDSS (mean (sd))	0.07 (0.86)	0.31 (0.89)	0.319
New T2 lesions on post-partum MRI (mean (sd))	1.20 (1.74)	2.05 (1.78)	0.082
Enhancing lesions (mean (sd))	0.30 (0.80)	1.10 (1.54)	0.034

New T2 lesions prior to conception (mean (sd))	0.89 (1.45)	1.45 (1.70)	0.22
Enhancing lesions pre-pregnancy (mean (sd))	0.68 (1.38)	0.43 (1.06)	0.431

Table 2: Odds ratio of model components that predict planned pregnancies

	Odds ratio (95% CI)
No family planning counseling	0.028 (0.0024, 0.20)
Married at first prenatal visit	17.4 (1.30, 664)
Age ≥ 30	13.9 (2.57, 105)
Prior pregnancy	0.20 (0.03, 1.03)

Table 3: Baseline between those who did and did not relapse while trying to conceive

	No Relapse	Relapsed	p-value
n	32	11	
Race (%)			0.041
Black	1 (3.1)	3 (27.3)	
Hispanic	3 (9.4)	0 (0.0)	
White	28 (87.5)	8 (72.7)	
Married (%)	0.97 (0.18)	11 (100)	0.564
BMI (mean (sd))	24.93 (4.29)	28.33 (8.72)	0.095
Smoking (%)	4 (12)	1 (9)	0.768
Pack years (mean (sd))	1.14 (2.90)	1.64 (2.91)	0.627
Age at diagnosis of MS (mean (sd))	26.77 (4.96)	29.27 (5.17)	0.16
Age at delivery (mean (sd))	32.70 (4.36)	34.00 (4.29)	0.398
Relapse after pregnancy (%)	23 (72)	8 (73)	0.958
Relapse one year post-partum (%)	15 (47)	6 (55)	0.67
Average ARR post-partum year (mean (sd))	0.59 (0.80)	0.82 (1.17)	0.481
Duration of MS (mean (sd))	5.94 (3.49)	4.73 (4.10)	0.349
Fertility drugs (%)	3 (9)	2 (18)	0.444
IVF (%)	1 (3)	1 (9)	0.43
Counselling (%)	30 (94)	11 (100)	0.408
On DMT (%)	2 (6)	1 (9)	0.757
DMT (%)	30 (93.5)	10 (90.9)	0.726
Betaseron	1 (3.1)	0 (0.0)	
Copaxone	1 (3.1)	1 (9.1)	
C-section (%)	12 (38)	7 (64)	0.139
Epidural anesthesia (%)	20 (62)	6 (55)	0.651
Spinal anesthesia (%)	6 (19)	4 (36)	0.243
Gestational age (mean (sd))	38.24 (1.78)	39.34 (1.13)	0.062
Age at menarche (mean (sd))	12.06 (1.30)	12.00 (1.20)	0.915
Gravida (mean (sd))	1.75 (0.95)	1.91 (1.30)	0.666
Term pregnancies (%)	28 (87.5)	11 (100.0)	0.529
Birth weight in kg (mean (sd))	3.06 (0.57)	3.34 (0.44)	0.158
Apgar score at 1 minute (mean (sd))	7.87 (1.71)	8.55 (0.69)	0.213
Pre-pregnancy EDSS (mean (sd))	1.53 (1.14)	1.95 (1.11)	0.289
New T2 pre-pregnant MRI (mean (sd))	1.41 (1.60)	1.55 (1.97)	0.827
Enhancing lesions on pre-pregnant MRI (mean (sd))	0.55 (1.19)	0.09 (0.30)	0.218
Post-partum EDSS (mean (sd))	1.88 (0.96)	2.18 (1.25)	0.402
New T2 on post-partum MRI (mean (sd))	1.90 (1.73)	2.45 (1.86)	0.373

Enhancing Lesions on post-partum MRI (mean (sd))	1.15 (1.61)	0.91 (1.30)	0.655

Table 4: Predictors of relapses while trying to conceive

	Relapsed	No relapse	p-value
N	11	32	
Time attempting to conceive in days (mean (sd))	322.73 (250.76)	106.41 (134.51)	0.001
Relapses the year prior to planning to conceive (mean (sd))	0.64 (0.81)	0.38 (0.71)	0.314
Discontinue DMT (%)	6 (55)	23 (72)	0.301
Type of DMT Discontinued (%)			0.491
None	5 (45.5)	9 (28.1)	
Injectable	4 (36.4)	18 (56.2)	
High Efficacy DMT	2 (18.2)	5 (15.6)	

Table 5: Odds ratio of model predicting relapse while attempting to conceive

	Odds Ratio (95% CI)	p-value
Time attempting to conceive in days	3.8 (1.43, 10.0)	0.007
Number of relapses in the year prior to planning for conception	2.69 (0.71, 10.2)	0.14
Last BMI pre-pregnancy	1.91 (0.75, 4.87)	0.171
Number of new T2 lesion on pre-pregnancy MRI	0.13 (0.02, 1.13)	0.064

Table 6: Baseline demographics comparing anesthesia choice in labor

	No Anesthesia	Epidural Anesthesia	Spinal Anesthesia	p-value
N	13	38	12	
BMI (mean (sd))	24.62 (5.69)	26.12 (7.56)	27.41 (5.94)	0.617
Age at delivery (mean (sd))	32.37 (4.12)	29.78 (7.77)	34.49 (5.02)	0.092
Duration of MS (mean (sd))	4.02 (2.62)	5.13 (3.75)	6.51 (4.08)	0.237
Race (%)				0.378
Black	1 (7.7)	2 (5.3)	2 (16.7)	
Hispanic	0 (0.0)	4 (10.5)	0 (0.0)	
White	12 (92.3)	32 (84.2)	10 (83.3)	
Maternal smoking during pregnancy (%)	3 (23)	7 (18)	1 (8)	0.618
Number of relapses the year prior to pregnancy (mean (sd))	0.62 (0.65)	0.53 (0.89)	0.83 (1.27)	0.612
Number of new T2 lesions on MRI prior to pregnancy (mean (sd))	1.46 (1.81)	1.47 (1.75)	0.50 (0.67)	0.185
EDSS pre-pregnancy (mean (sd))	1.85 (1.52)	1.76 (1.14)	1.58 (1.02)	0.855
Number of enhancing lesions on MRI pre-pregnancy (mean (sd))	0.15 (0.38)	0.72 (1.39)	0.25 (0.87)	0.224
Planned pregnancy (mean (sd))	0.69 (0.48)	0.66 (0.48)	0.75 (0.45)	0.84
On DMT (mean (sd))	0.31 (0.48)	0.29 (0.46)	0.17 (0.39)	0.676
Complications (mean (sd))	0.15 (0.38)	0.37 (0.49)	0.33 (0.49)	0.366

Complication Type (%)				0.875
Abruption	0 (0.0)	1 (2.6)	0 (0.0)	
Arrest of Labor	1 (7.7)	2 (5.3)	1 (8.3)	
Fetal heart rate	0 (0.0)	1 (2.6)	0 (0.0)	
Gestational diabetes	0 (0.0)	1 (2.6)	0 (0.0)	
Hemorrhage	0 (0.0)	1 (2.6)	0 (0.0)	
Malpresentation	0 (0.0)	3 (7.9)	3 (25.0)	
None	11 (84.6)	25 (65.8)	8 (66.7)	
Preterm premature rupture of the membrane	0 (0.0)	2 (5.3)	0 (0.0)	
Preeclampsia	1 (7.7)	2 (5.3)	0 (0.0)	
C-section (%)	3 (23)	9 (24)	12 (100)	<0.001
Gravida (mean (sd))	1.38 (0.77)	1.82 (1.09)	2.33 (1.23)	0.09
Term (mean (sd))	0.46 (0.52)	0.32 (0.57)	0.58 (0.51)	0.315
Pre-term (mean (sd))	0.00 (0.00)	0.03 (0.16)	0.00 (0.00)	0.726
Abortion (mean (sd))	0.08 (0.28)	0.53 (0.86)	0.58 (1.00)	0.189
Living (mean (sd))	0.38 (0.51)	0.31 (0.58)	0.09 (0.30)	0.368
Breastfeed (%)	7 (54)	18 (47)	8 (67)	0.516
Duration of breastfeeding in days	140 (158)	93 (127)	89 (64)	0.644

Table 7: Measure of post-partum disease activity by anesthesia type

	No Anesthesia	Epidural Anesthesia	Spinal Anesthesia	p
N	13	38	12	
Time to restart DMT days (mean (sd))	174 (153)	204 (342)	76 (51)	0.569
Time to relapse in days, (mean (sd))	638 (798)	643 (800)	551 (589)	0.934
Number of relapses the year after (mean (sd))	0.54 (0.52)	0.68 (0.90)	0.58 (0.90)	0.841
EDSS at first post-partum visit (mean (sd))	2.00 (1.57)	2.03 (1.07)	1.83 (0.75)	0.876
Change from pre-pregnancy EDSS to post-partum EDSS (mean (sd))	0.15 (0.88)	0.26 (0.93)	0.25 (0.78)	0.929
Number of new T2 lesions on post-partum MRI (mean (sd))	2.15 (1.86)	1.65 (1.81)	1.64 (1.80)	0.674
Number of enhancing lesion on post-partum MRI (mean (sd))	0.62 (1.19)	0.89 (1.43)	1.00 (1.61)	0.775

Figures

Figure 1: Inclusion and exclusion criteria.

Figure 2: Proportion of planned pregnancies depending on whether the patient received family planning counseling.

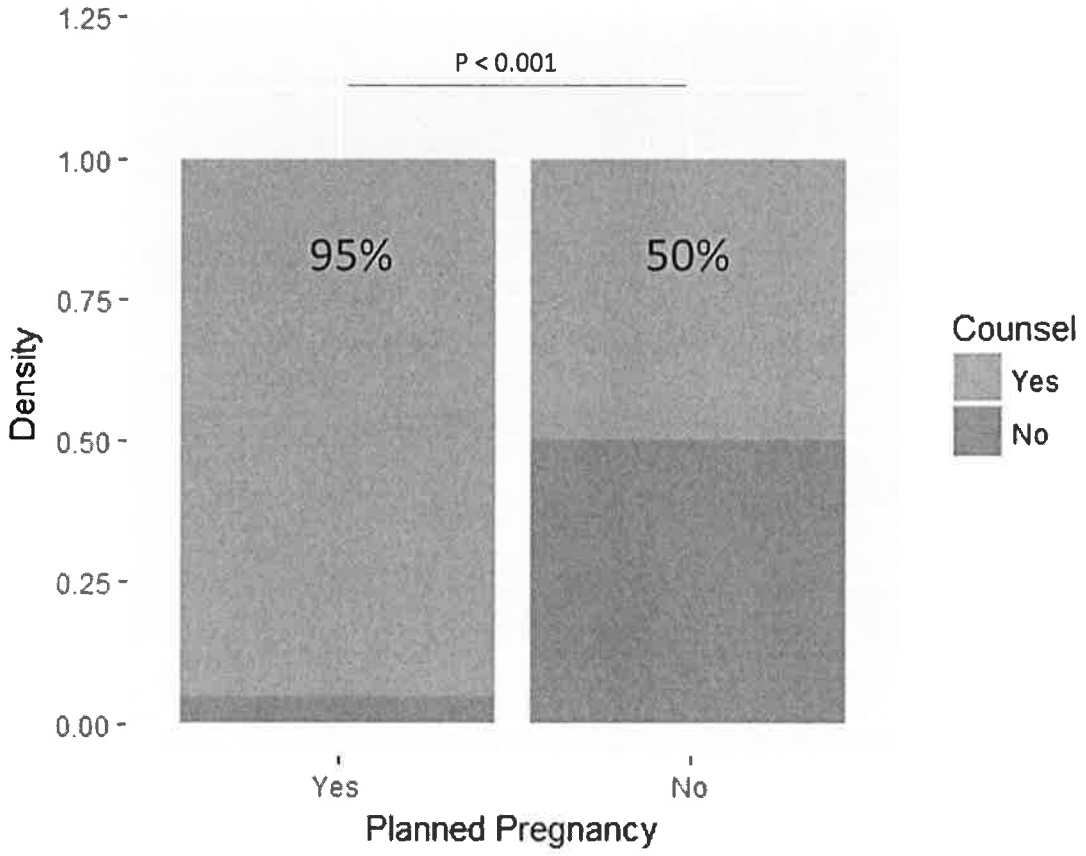


Figure 3: Proportion of planned pregnancies based on age.

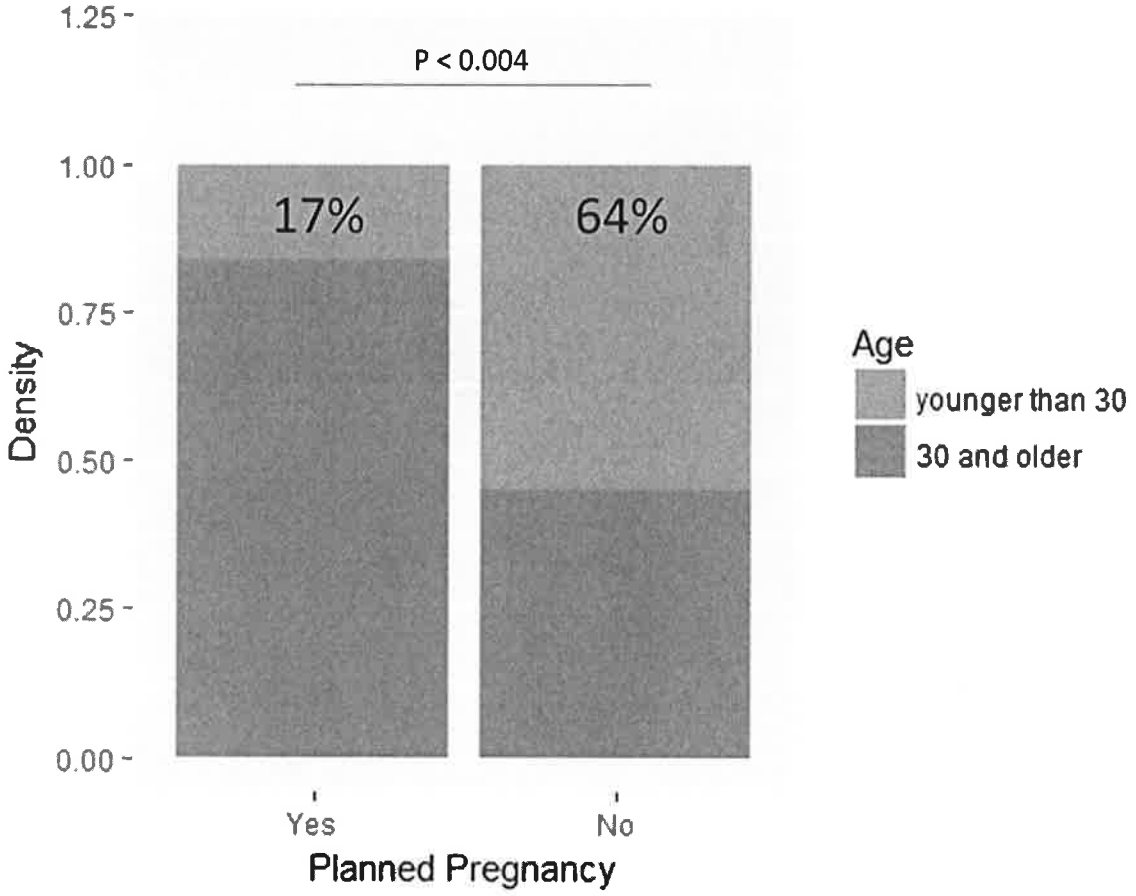


Figure 4: Proportion of planned pregnancies based on marital status.

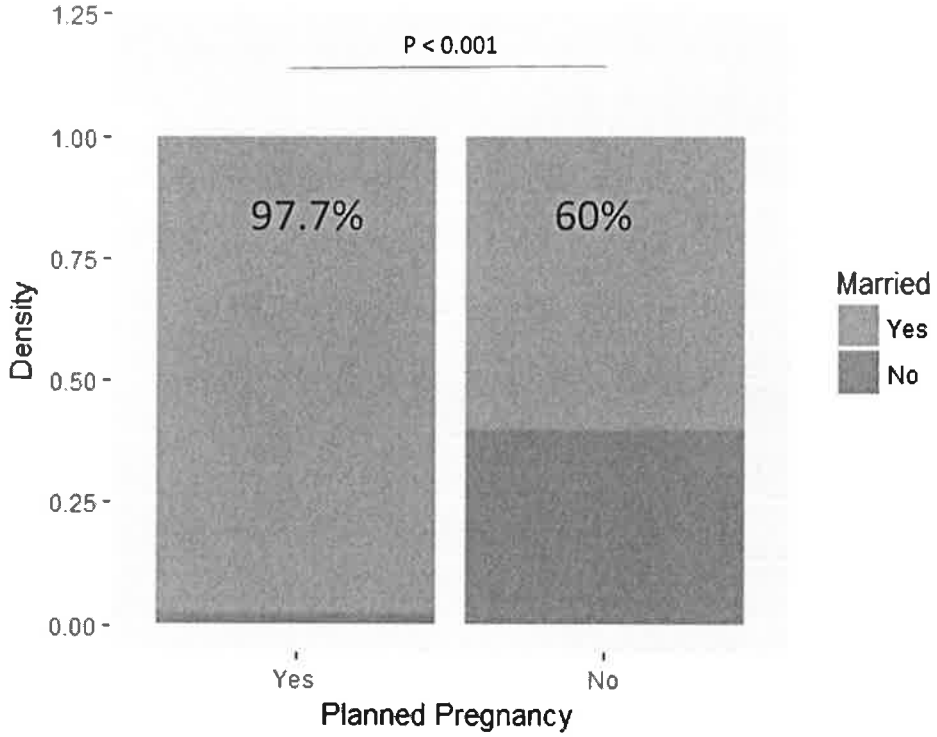


Figure 5: Odds ratios for unplanned pregnancy from the complex post stepwise regression model predicting planned pregnancies. The triangle represents the odds ratio, dark blue line represents 90% confidence interval, medium blue line represents 95% confidence interval, and light blue line represents 99% confidence interval.

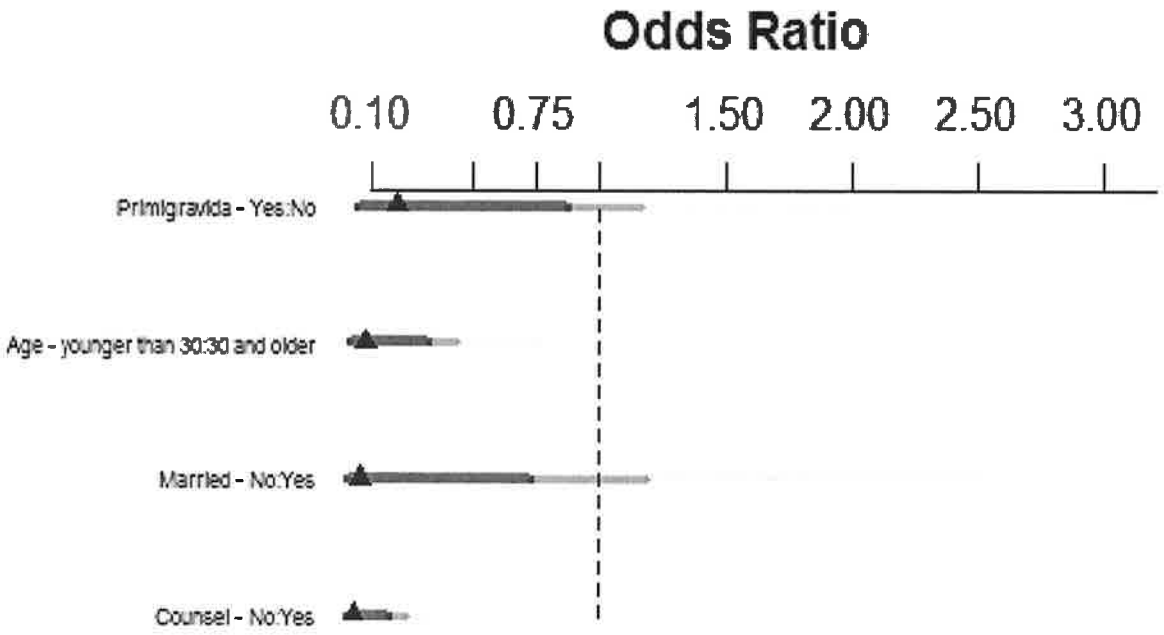


Figure 6: Proportion of individuals on DMT depending upon their pregnancy status.

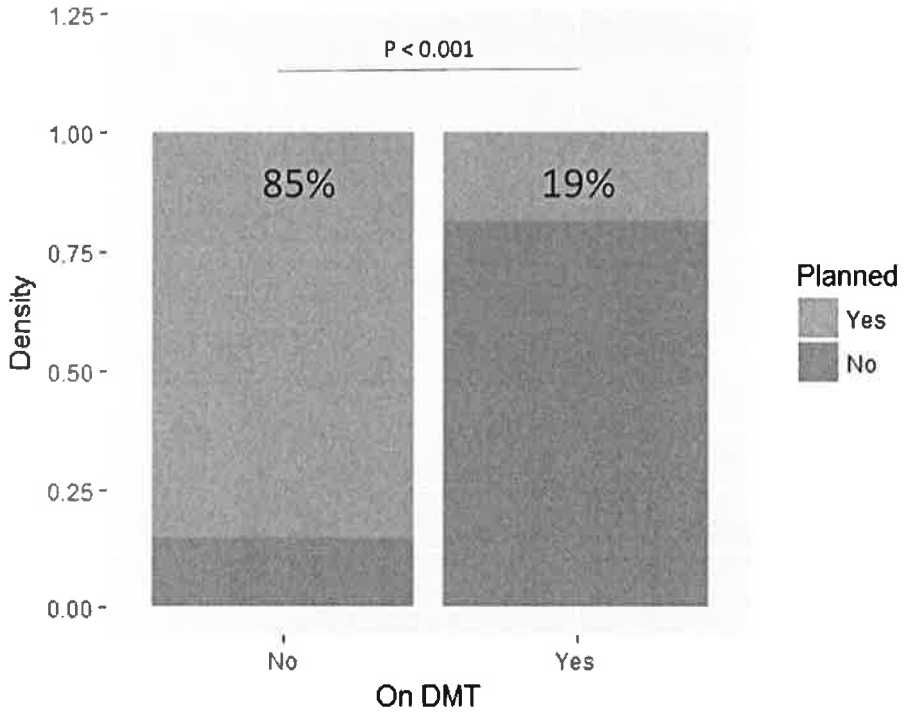


Figure 7: Days attempting to conceive in patients that did or did not relapsed.

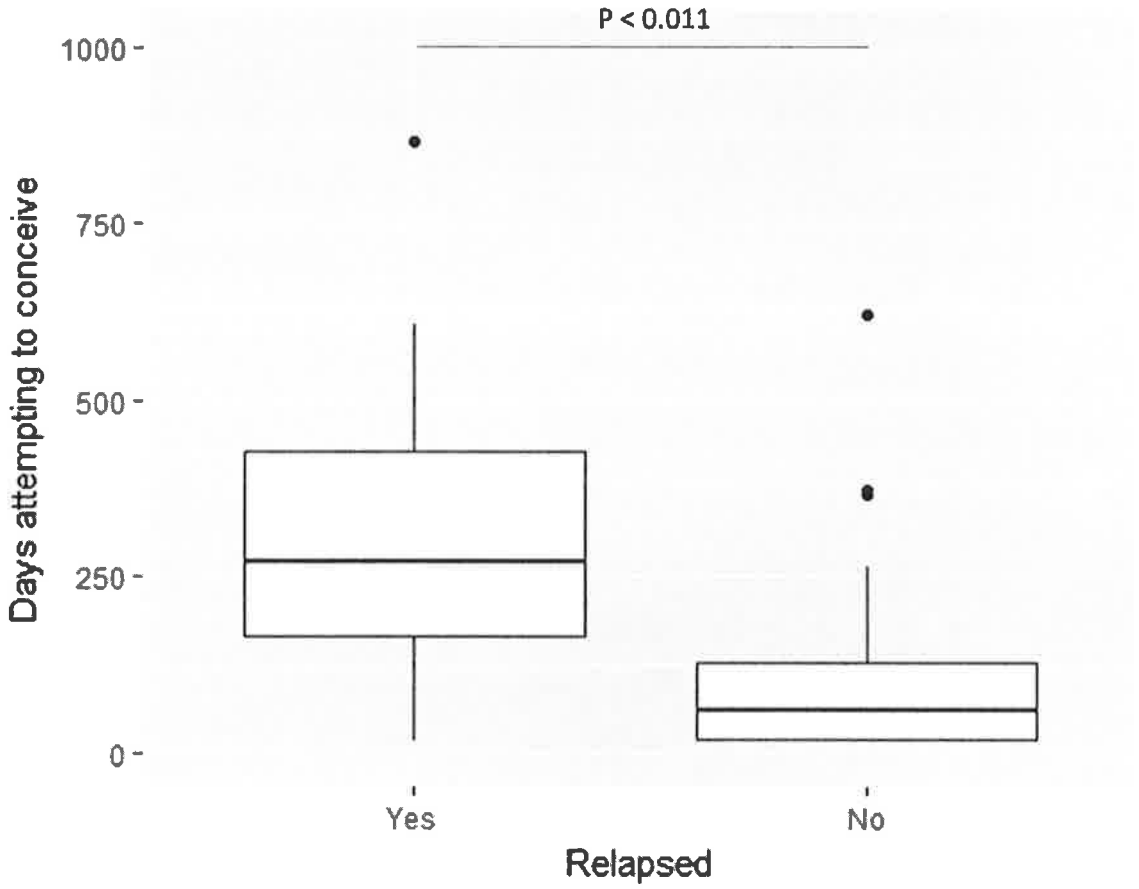


Figure 8: Odds ratio of having a relapse while attempting conception. The triangle represents the odds ratio, dark blue line represents 90% confidence interval, medium blue line represents 95% confidence interval, and light blue line represents 99% confidence interval.

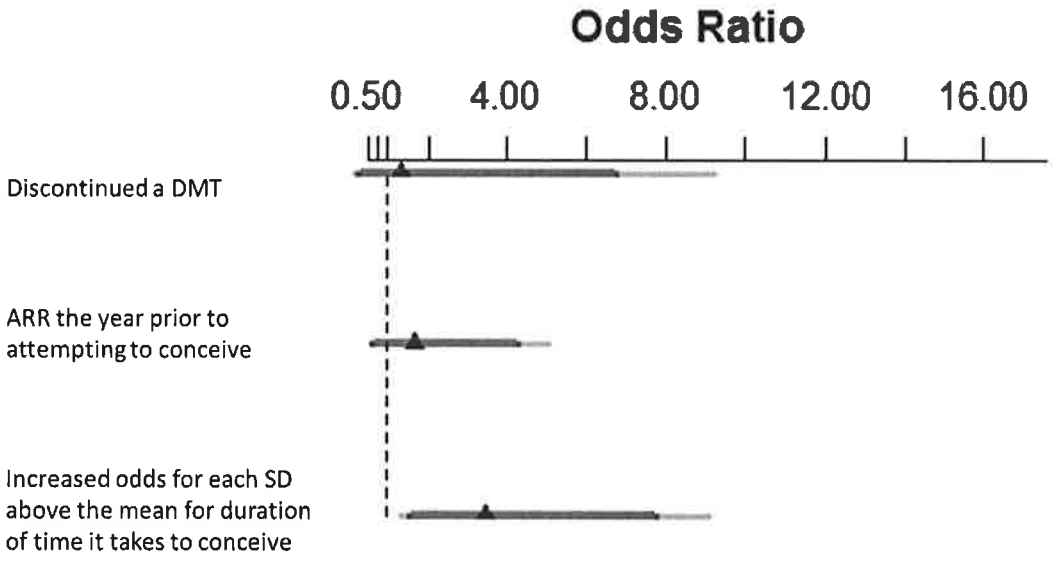


Figure 9: Time to relapse separated by anesthesia used during labor and delivery

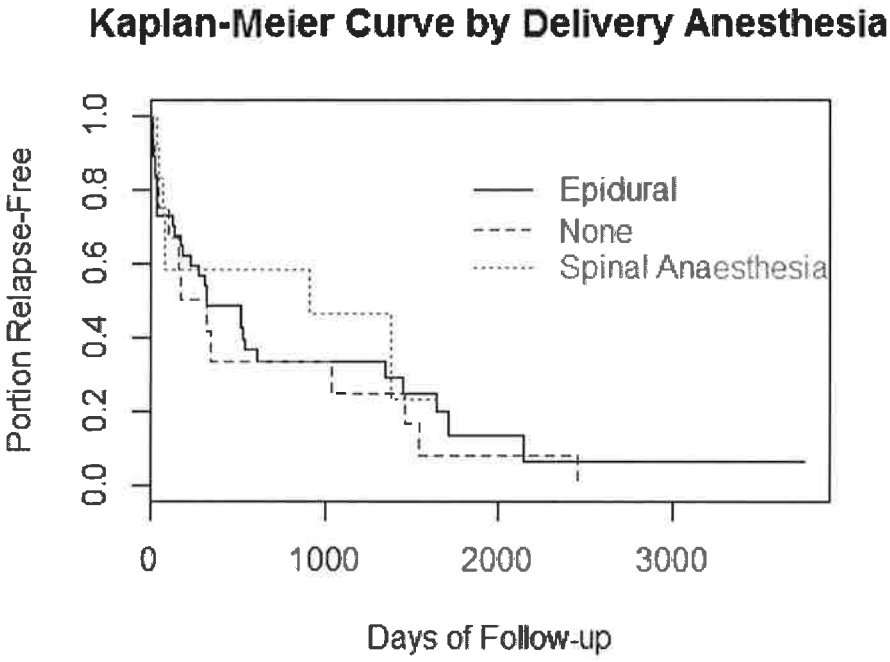


Figure 10: Number of relapses in the post-partum(PP) year by delivery anesthesia groups (epidural anesthesia (EA), spinal anesthesia (SA), and no anesthesia (NA))

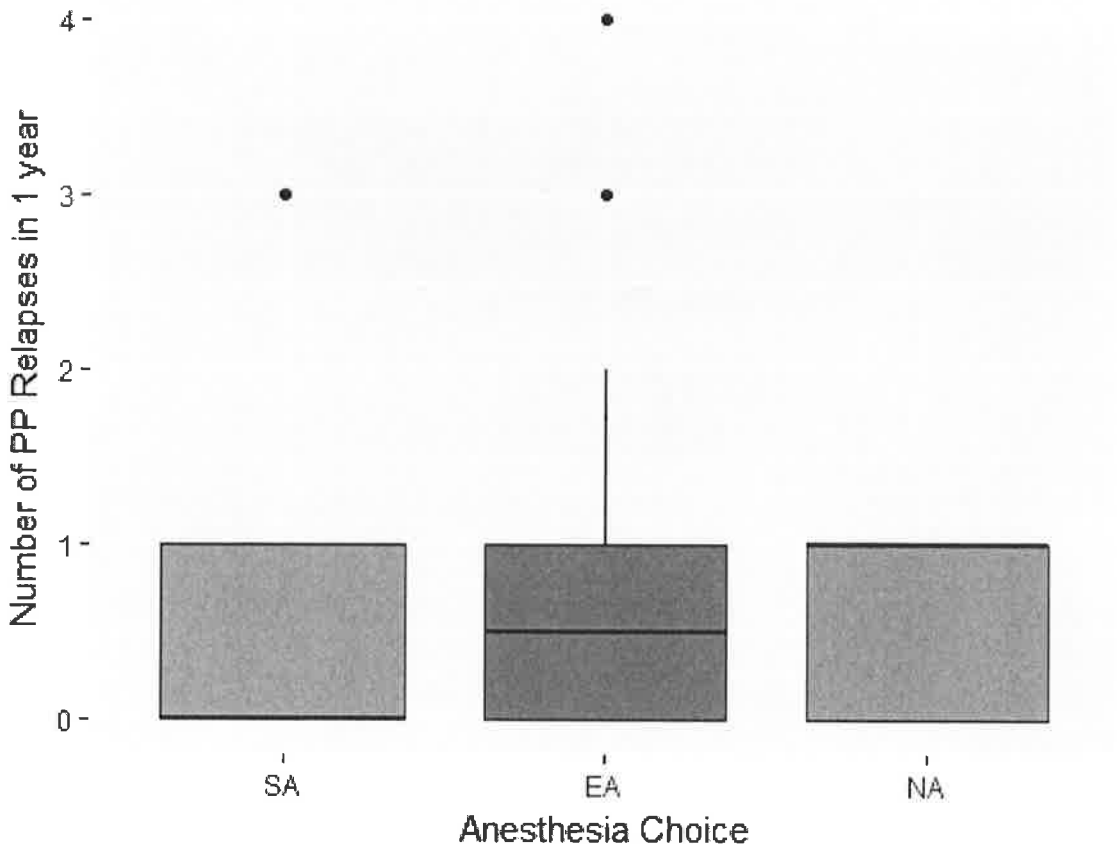


Figure 11: Number of enhanacing lesions on first post-partum(PP) MRI by delivery anesthesia groups (epidural anesthesia (EA), spinal anesthesia (SA), and no anesthesia (NA))

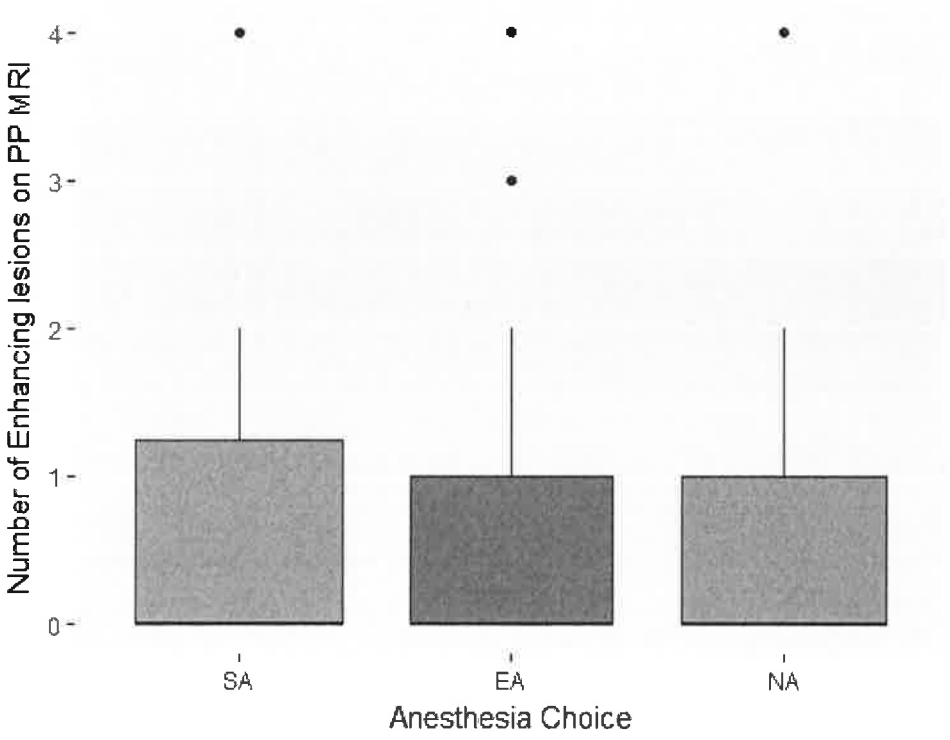


Figure 12: Number of new T2 lesions on the post partum (PP) MRI by delivery anesthesia groups (epidural anesthesia (EA), spinal anesthesia (SA), and no anesthesia (NA))

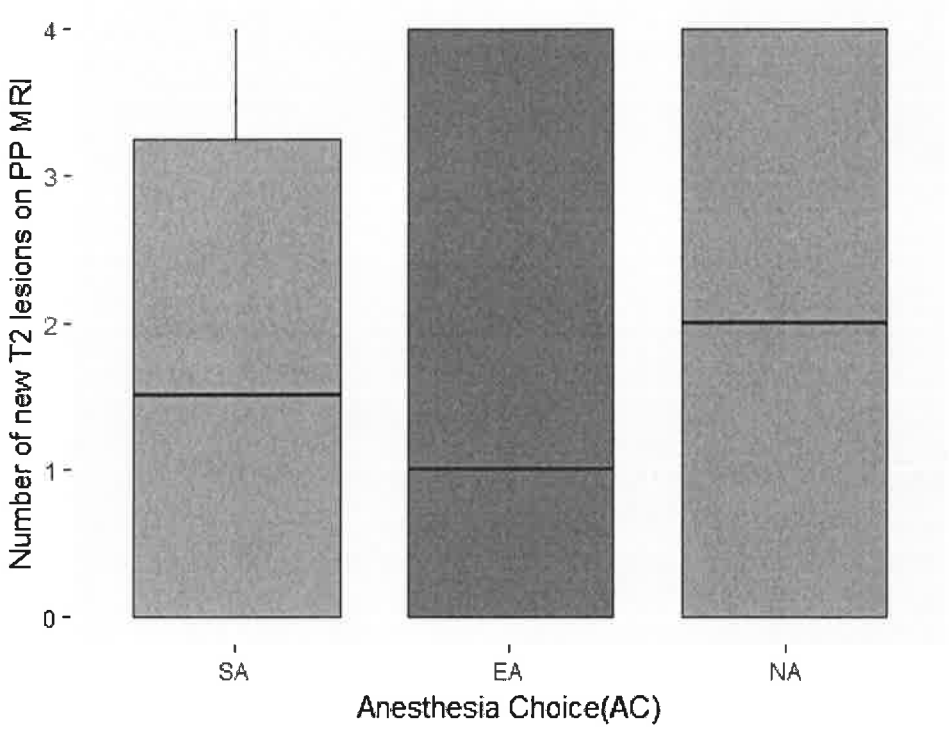
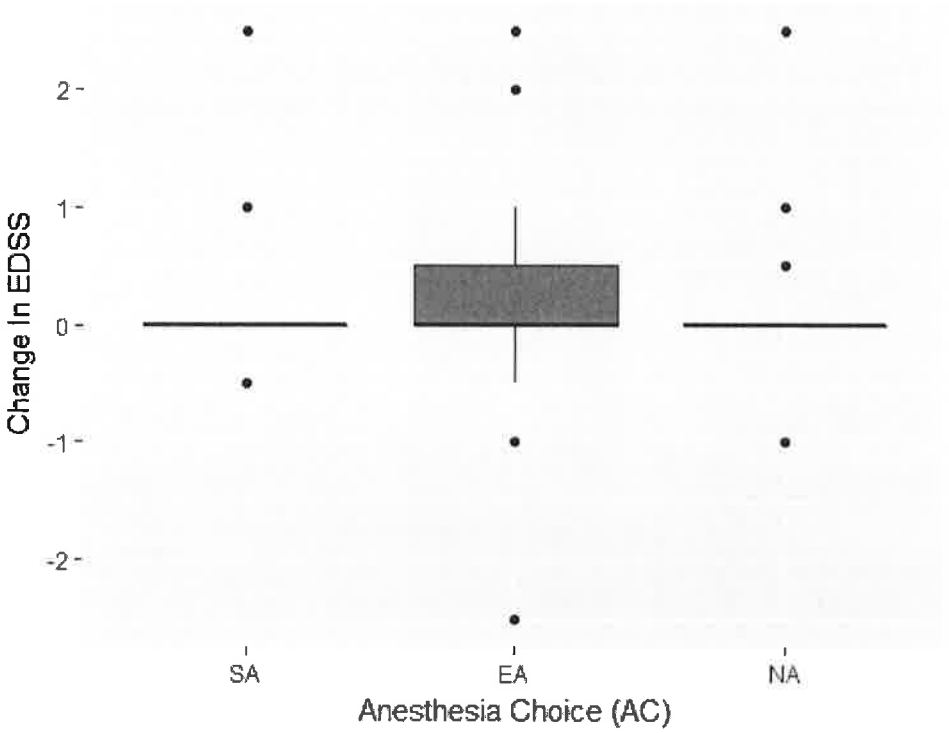


Figure 13: Net change in pre and post pregnancy EDSS by delivery anesthesia groups (epidural anesthesia (EA), spinal anesthesia (SA), and no anesthesia (NA))



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