The University of Nebraska Medical Center

Department of Obstetrics and Gynecology

34th Annual

Resident Research Day

Wednesday, June 4th, 2021
Eppley Science Hall
Room 3010

UNMC Department of Obstetrics and Gynecology

34th Annual Residents' Research Day

June 4, 2021

Schedule of Events

Eppley Science Hall - Room 3010

8:30 am

Welcome to Resident Research Day!

Dr. Carl Smith & Dr. Jean Amoura

	Presenter	Title of Project
8:45	**Liz Kastrick, MD, HOI** **Advisor: Mel Mathes, MD**	"Trikafta Contraceptive Counseling and Practices"
9:00	**Gerson Manriquez, MD, HOI** **Advisor: Karen Carlson, MD**	"Outpatient Cervical Ripening: Friend or Foe?"
9:15	**Jordan McColm, MD, HOI** **Advisor: Jean Amoura, MD**	"Assessment of Cervical Epithelium in Trans Men Undergoing Hysterectomy"
9:30	**Sydney Randall, MD, HOI** **Advisor: Kelsie Cabrera, MD**	"Improving Ankyloglossia Identification and Management Via Frenotomy at Nebraska Medicine: A Quality Improvement Project"
9:45	**Macy Walz, MD, HOI** **Advisor: Amie Hollard, MD**	"Fetal Growth Restriction Outcomes Defined by Estimated Fetal Weight vs Isolated Abdominal Circumference"
10:00: 30-minute break, please view the posters of completed projects in the lobby		
10:30	**Alissa Burchell, MD, HOIV** Advisor: Joshua Dahlke, MD	"Evaluation of the Clinical Use of Antenatal Corticosteroids in Late Preterm Women at Risk for Preterm Delivery"
10:45	**Anna Gorman, DO, HOIV** Advisors: Joshua Dahlke, MD &Sonja Kinney, MD	"The Impact of 'Meds to Beds' on Postpartum Opioid Use"
11:00	**Melissa Mathes, MD, HOIV** Advisor: Stephanie Gustin, MD	"How Low is Too Low? Post-wash Total Motile Sperm Count Effect on Pregnancy Outcomes in Intrauterine Insemination"
11:15	**Garth Summers, DO, HOIV** Advisor: Stephanie Gustin, MD	"Does GnRH Agonist Treatment in Patients with Abnormal Expression of BCL6 and/or Beta 3 Integrin Restore Implantation Rates to a Comparative Level with Those Patients Without Known Endometrial Receptivity Abnormalities? An Interim Analysis."
11:30	**Taylar Swartz, DO, HOIII** Advisor: Katherine Lessman, MD	"A Call for More Holistic Approaches: Physician Mothers' Responses to the Lived Experience of Early Pregnancy Loss"
11:45: Conclusion		

Trikafta Contraceptive Counseling and Practices

Elizabeth Kastrick, MD, HO1

Advisor: Melissa Mathes, MD

Introduction: Trikafta is a triple drug therapy combination of elexacaftor-tezacaftor-ivacaftor designed for individuals with cystic fibrosis and specific related gene mutations, including F508del mutation. Trikafta was approved for use in the United States in 2019 for the treatment of cystic fibrosis (CF). Infertility is commonly associated with CF. There is known improvement in fertility for female patients on Trikafta, although there is no formal contraceptive counseling at our institution for these patients. The goal of this project is to address the absence of adequate patient counseling regarding contraception, fertility, and pregnancy outcomes.

Objective: To describe the current state of contraceptive counseling and practices in women with cystic fibrosis who are currently taking Trikafta.

Study Design: This is a descriptive study evaluating approximately 150 female patients within the Children's Hospital and Nebraska Medicine hospital systems who have cystic fibrosis and are currently taking Trikafta. Patients included in this study would receive a one-time, anonymous, multiple choice patient survey at the time of their upcoming clinic visit. Exclusion criteria: individuals under 19 years of age with a parent who did not consent to completing this survey, children under the age of 14, and individuals greater than 65 years of age. The information gathered from this survey will include information regarding the patient's age, reproductive history, past and current contraceptive management, contraceptive knowledge, reproductive goals, and if the patient has received counseling on safe sexual practices and management.

Results:

Descriptive data will be expressed with mean and standard deviation. I intend to analyze the patient questionnaire results to determine if counseling for contraception and preconception management is occurring, if there is an optimal time when counseling should occur, and if patients are receiving adequate preconceptive counseling based on reproductive goals. I anticipation the results of this study will reveal the absence of adequate patient counseling regarding contraception, fertility, and pregnancy outcomes for those patients currently taking Trikafta.

Conclusions:

This study described the absence of contraceptive counseling in women with cystic fibrosis who are currently taking Trikafta. I anticipate that there is a need for counseling for this unique patient

population and that standardizing counseling would improve patient care and outcomes. This quality improvement project further supports the implementation of standardized contraception, fertility and pregnancy counseling. A subsequent study could be undertaken regarding the instillation of gynecologic evaluation prior to patients initiating Trikafta as well.

Outpatient Cervical Ripening; Friend or Foe?

Gerson Manriquez, MD, HOI
Advisor: Karen Carlson, MD

Introduction: The rate of induction of labor is on the rise in the 21st century. This process can mean several hours but even days spent in the hospital prior to delivery. Both mechanical and pharmacological options exist as options for cervical ripening in someone with an unfavorable cervix. These patients are typically managed as an inpatient. With some of these prolonged hospital admissions though, one can encounter patient dissatisfaction, financial burden and even staffing concerns. In selected individuals, outpatient cervical ripening can be an option as it has been shown to be both safe, effective and has the potential to even increase patient satisfaction, reduces workload and potentially decrease hospital stay cost.

Objective: Assess and compare patient's satisfaction and experience with outpatient vs inpatient transcervical balloon cervical ripening management to better inform our practice moving forward

Study Design: An outpatient transcervical balloon cervical ripening protocol has been established. Eligible patients will need to meet inclusion criteria for outpatient management. Patients who are eligible will then be sent to labor and delivery for foley balloon placement. A survey will be administered during the check in process, a post survey will be administered when they return. Outpatient management patients will auto self-select. A pre and post survey will also be administered to the population that got an foley balloon catheter for cervical ripening while inpatient.

Results: Plan is to analyze satisfaction score. Additional data will be gathered such as: demographics of our patient population, time from insertion to delivery, time at home vs hospital, cesarean rate % and compare them to patients with similar inclusion criteria but who received transcervical foley balloon and managed as an inpatient.

Conclusions: I hypothesize that patient satisfaction will be overall greater in the outpatient cervical ripening branch group vs inpatient cervical ripening. If this is the case, there should be a greater emphasis in offering this option to the right candidates at UNMC. This can be a way to attract more patients to our hospital system.

Transgender male cervical epithelial thickness on total laparoscopic hysterectomy specimens

Jordan McColm, MD, HOI

Advisor: Jean Amoura, MD and Subodh Lele, MD

Introduction: Vaginal epithelial thickness has been shown be decreased in post-menopausal versus pre-menopausal women due to the decrease in sex hormones, specifically estrogen. Vaginal atrophy has been shown to be a risk factor for cuff dehiscence following hysterectomies. This same principle has not been researched in transgender male patients on testosterone therapy which also decreases estrogen and has been shown to alter the vaginal epithelium in multiple ways including decreasing epithelial thickness.

Objective: The purpose of this study is to define cervical epithelial thickness on total laparoscopic hysterectomy specimens from transgender male patients on testosterone therapy and compare this thickness to cis-gender premenopausal women, post-menopausal women, and post-menopausal women on hormone replacement therapy.

Study Design: This is a retrospective study using archived pathology slides of cervical cross-sections from total laparoscopic hysterectomy specimens. The vaginal cuff is not present on total laparoscopic hysterectomy specimens so the cervical epithelial thickness will be used as a substitute. The cervical epithelium will be measured at the thinnest point using microscopic camera software with built in measuring scale. The goal is to measure cervical epithelial thickness in all four populations and compare these looking for statistically significant differences between the populations.

Results: The anticipated result is that transgender male patients on testosterone therapy and post-menopausal women will have similar cervical epithelial thickness as will pre-menopausal women and post-menopausal women on hormone replacement therapy.

Conclusions: This data can hopefully be applied in the future when assessing for increased risk for post-operative complications of total laparoscopic hysterectomy including cuff dehiscence. If testosterone in these patients is a risk factor, then the use of pre-operative vaginal estrogen to decrease risk could be considered. This has been looked at in post-menopausal women undergoing hysterectomy and has been shown to increase epithelial thickness at time of surgery. This has not been directly correlated to lower rates of cuff dehiscence.

Improving ankyloglossia identification and management via frenotomy to improve breastfeeding outcomes: a quality improvement project.

Sydney Randall, MD, HOI

Advisor: Kelsie Cabrera, DO

Introduction: Ankyloglossia, also known as "tongue tie", is a condition that has been thought to have a detrimental effect on infant breastfeeding. Frenotomy, the process of releasing a tongue affected by ankyloglossia, has been used as a method of improving latch and breastfeeding outcomes. There is not a current consensus on how to evaluate ankyloglossia or incorporate the use of frenotomy in the immediate postpartum period at Nebraska Medicine, which could contribute to poorer breastfeeding outcomes for mother and infant.

Objective: To implement a tool to objectively identify and grade ankyloglossia in order to allow for inpatient management via frenotomy. The overall goal of this quality improvement project is to improve mother and infant breastfeeding outcomes at Nebraska Medicine.

Study Design: Different assessment tools used in the evaluation of ankyloglossia were reviewed and the Bristol Tongue Tie Assessment tool was selected to implement as an objective means of grading ankyloglossia. Lactation consultants at Nebraska Medicine currently use the LATCH assessment tool to grade infants that are having difficulties with breastfeeding. If an infant's score on the LATCH assessment tool is suboptimal, the Bristol tool will be implemented to objectively score the level of ankyloglossia. This will help medical providers determine whether frenotomy would be indicated as an early intervention prior to postpartum discharge from the hospital. To further aid in early intervention, a list of current providers that perform frenotomy on infants will be distributed to lactation consultants so that the inpatient frenotomy procedure can be coordinated more easily.

Results: Once successfully implemented, this tool for grading tongue tie will provide lactation consultants an objective rather than only a subjective way to grade ankyloglossia. This will help identify those patients that would benefit from frenotomy. Implementation of an organized call system of providers that perform frenotomy will allow patients to have ankyloglossia addressed more quickly after birth, ideally prior to postpartum discharge from the hospital. This will help avoid the need for further outpatient evaluation and management.

Conclusions: Implementing an objective grading tool to assist in evaluation will help to keep the management of ankyloglossia with frenotomy consistent at Nebraska Medicine. It will also give providers an objective way to determine if frenotomy would be beneficial for mothers and infants. Providing earlier intervention and management of ankyloglossia with frenotomy has the potential to improve the early breastfeeding relationship and therefore overall breastfeeding outcomes at Nebraska Medicine. This can be especially beneficial for those patients for which outpatient coordination of the procedure is difficult or not an option.

Fetal Growth Restriction Outcomes Defined by Estimated Fetal Weight vs Isolated Abdominal Circumference

Macy Walz MD, HOI

Advisor: Amie Hollard MD, MFM

Introduction: Variation exists worldwide on the definition of Fetal Growth Restriction (FGR). Many studies have been performed to determine how to most accurately diagnosis FGR. Based on these studies, SMFM has updated their FGR guidelines in 2020 to include a diagnosis of FGR as EFW $<10^{th}$ percentile isolated AC as $<10^{th}$ percentile. Using an isolated AC of $<10^{th}$ has been shown to more accurately predict SGA. The outcomes of these fetuses have not been studies.

Objective: To investigate neonatal outcomes in fetuses diagnosed with FGR based on EFW$<10^{th}$ or AC $<5^{th}$ versus isolated AC measurements of 5^{th}-10^{th} as compared to normally grown fetuses.

Study Design: A retrospective cohort study of non-anomalous singleton gestations who underwent a third trimester growth ultrasound and delivered at University of Nebraska Medical Center from July 2007 until May 2020. EFW and AC percentiles were based on Hadlock formula. Study groups are categorized based on definition of FGR. Group one includes fetuses diagnosed with FGR based on EFW of $<10^{th}$ percentile and/or isolated AC of $<5^{th}$ percentile. Group two includes fetuses diagnosed with FGR based on AC measurement $<10^{th}$ and $>5^{th}$ percentile. The control group is comprised of normally grown fetuses with EFW and AC $>10^{th}$ percentile. Study group one was managed based on typical FGR protocol with scheduled delivery based on severity of FGR and UA doppler findings. Group two was managed as a normally grown fetuses. Similarly, the control group was managed expectantly based on usual obstetric induction. Outcomes to be evaluated include GA at time of delivery, indication for delivery, mode of delivery, NICU admission or interventions for FGR complications, APGARs, cord gasses, neonatal demise, and birth weight/percentile. Data will be analyzed with the use of an ANOVA test with significance defined at $p < 0.05$.

Results: Study groups will be compared first to each other and the control group. We hypothesize that the overall number of FGR cases will increase with the use of AC $<10^{th}$ percentile as part of the diagnostic criteria. In addition, we believe the FGR fetuses based on AC $<10^{th}$ but $>5^{th}$ percentile will overall have better outcomes compared to traditionally diagnosed FGR fetuses.

Conclusions: Our study will evaluate the diagnosis rate of FGR. We will also evaluate if the diagnostic criteria for FGR will improve the obstetric and neonatal outcomes for fetuses with FGR based on AC measurement alone. The results of our study will help to determine the clinical significance of FGR diagnosis and if adopting the new criteria of AC $<10^{th}$ will benefit the patient populations studied.

Implementation of Preoperative Treatment for Bacterial Vaginosis in Patients Undergoing Hysterectomy

Anna Adamson, MD, HO2

Advisors: Jennifer Griffin-Miller, MD, MPH and Jean Amoura, MD, MSc

OBJECTIVE: The purpose of this study is to determine the rate of decolonization of *G. vaginalis* prior to surgery, following the institution of a standardized preoperative treatment, assuming a 30% prevalence rate without treatment.

METHODS: Bacterial vaginosis (BV) is a common condition caused by growth of *Gardnerella vaginalis* and affects an estimated one third of reproductive age women. While BV can cause vaginal discharge and malodor, many women with this infection remain asymptomatic. In those undergoing hysterectomy, the rate of postoperative vaginal cuff infection is higher in patients who have preoperative BV compared to those without BV. This association is further supported by the fact that *G. vaginalis* is commonly isolated from patients who have postoperative vaginal cuff infections. The advent of standard preoperative protocols (such as ERAS – enhanced recovery after surgery) presents an opportune time to implement treatment in preparation for surgery. Each patient will receive a three-day course of metronidazole 500mg BID as part of the ERAS kit that is provided pre-surgically. Patients will be instructed to complete this course of antibiotics in the week leading up to surgery. On the day of surgery, the patient will be asked if she completed all, part, or none of the prescribed antibiotic course. This will allow compliance rates to be quantified. A vaginal pathogen swab will then be obtained immediately prior to surgery to assess for effective decolonization of *G. vaginalis.* If a three-day course successfully decreases the rate of colonization, the rate of post-operative vaginal cuff infection prior to and after implementation of this model could be quantified. Though this would likely entail a much longer implementation period. The initial study period will be November 2020 through November 2021. This will include approximately 200 patients. Based on a 30% prevalence rate of BV, 300 patients will provide sufficient data in order to see a decrease in the rate of BV, if present. The primary outcome will be the rate of bacterial vaginosis in the study population following institution of this standardized pre-operative treatment. The secondary outcome will be the rate of patient compliance with taking the prescribed medication course.

RESULTS: Study in process

CONCLUSION: This study has the ability to influence future practice management in regards to presurgical treatment by providing a standard protocol. Postoperative infections cause patient and provider distress, increased risk of further complications, and increased total recovery time. Thus, implementation of a model that decreases the rate of postoperative vaginal cuff infections would benefit both patients and institutions.

Prevalence and clinical significance of post-translational RNA modifications in patients with Uterine Leiomyoma

Rosa Cancino, MD, HOII

Advisors: Jitu Wilson George, PhD and John Davis, PhD

Introduction: Uterine fibroids are monoclonal tumors that arise from the uterine smooth muscle. They comprise the most common gynecologic uterine tumors with a prevalence of 70-80% by 50 years of age, depending on race. Although most fibroids are asymptomatic, 20-25% of women with fibroids suffer from clinically significant symptoms including abnormal uterine bleeding, pelvic pressure, urinary complaints, constipation, recurrent pregnancy loss and infertility. Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterine artery embolizations are performed annually in the United States to aid in treatment of uterine leiomyomas. There appears to be a strong racial disparity in the disease with African American women having a higher incidence, larger tumors at diagnosis, more severe symptoms and earlier age at diagnosis than Caucasian, Hispanic or Asian American women. Somatic mutations in the form of Mediator Complex protein 12 (MED12) gene and overexpression of high mobility group AT hooks (HMGA)1/2 transcription factors are common in fibroids, however exact mechanisms of fibroidogenesis are unknown.

Objective: The purpose of this study is to characterize post-transcriptional modifications of small RNA in uterine fibroids and normal myometrium to identify possible molecular mechanisms for the disparity between black and non-black women.

Study Design: To analyze post-transcriptional differences in RNA, 1g samples of normal myometrium and endometrium and 1g samples of fibroid from each sample will be collected. Inclusion criteria for normal myometrium and endometrium includes: myometrium and endometrium taken from abdominal or laparoscopic hysterectomy samples without pathology (fibroids or cancer). Inclusion criteria for fibroid myometrium and endometrium includes: normal and fibroid endometrium and myometrium from abdominal and laparoscopic hysterectomy samples with fibroid diagnosis but without further pathology (cancer). Additionally, we will collect clinical information including age, race/ethnicity, BMI, age of menarche, parity, reason for hysterectomy, fibroid number, and fibroid size associated with the patient who provided these samples. To genetically characterize fibroids by MED 12 mutations /HMGA2 expression DNA from the non-fibroid and fibroid myometrium will be isolated using Qiagen DNeasy Blood & Tissue kits. Isolated DNA will then be amplified using PCR against MED12 primers and Sanger sequenced. Total and small RNA will be isolated using mirVana miRNA isolation kit. RT-qPCR will be performed against HMGA2/1 primers to identify amplification. Following isolation of small RNA, the samples will be treated with NEB nucleoside digestion mix and sequenced. Once these mutations have been identified, the clinical characteristics of affected patients will be compared.

Results: The prevalence of sRNA modifications in our sample will be tallied and Pearson's chi-squared test will be used to determine if these mutations are clinically significant when present in fibroid myometrium in relation to normal myometrium.

Conclusions: By comparing molecular expression differences in normal uterine myometrium and uterine fibroids, we aim to determine if certain sRNA mutations are more prevalent in black women when compared to other groups. It is important to continue to identify differences in molecular expression, as their identification could allow for development of new treatment options in the age of targeted therapy.

Use of Endocrine Therapy for Breast Cancer Reduction in Patients with Atypical Hyperplasia or Lobular Carcinoma in Situ: From Diagnosis to Discussion

Kassie Frith, DO HO2

Advisor: Jennifer Griffin, MD

Introduction: In 2013, the US Preventive Services Task Force (USPSTF) and ASCO updated their recommendations for the use of breast cancer risk reduction medications in women with an elevated risk of breast cancer or those with Lobular Carcinoma In Situ (LCIS). These recommendations are also supported by the National Comprehensive Cancer Network (NCCN).

Despite evidence of clinical benefit, the uptake of endocrine therapy for breast cancer reduction is low. Studies have shown prescribing risk reduction medication is strongly associated with ease of determining high-risk eligibility among other factors, thus making a pathologic diagnosis of breast atypia or LCIS an easy target for improving access.

At UNMC, the prevalence of either the discussion or the initiation of endocrine therapy for breast cancer risk reduction in patients diagnosed with breast atypical or LCIS has not been well studied and it remains unclear as to which physician specialty should be discussing and monitoring endocrine therapy.

Objective: The goal of this study is to evaluate and implement a path for patients status post biopsy with results of atypical hyperplasia or lobular carcinoma in situ to receive adequate counseling and appropriate follow-up for initiation of endocrine therapy by identifying specialties with increased discussion and uptake rates.

Study Design: The records of consecutive patients with breast biopsy and pathologic findings of atypical hyperplasia or lobular carcinoma in situ who were treated at the authors' institution between Jan 2014 and Dec 2019 will be obtained from the EMR and analyzed. Whether patients were offered endocrine therapy, accepted endocrine therapy, and the associated reasons via chart review will be recorded. The type of provider discussing therapy will be noted in addition to what type of provider has provided follow-up in patients who initiate endocrine therapy. Differences will be evaluated using chi-square analysis.

Results: We will identify the rates of discussion of endocrine therapy for all patients diagnosed with atypical hyperplasia or lobular carcinoma in situ in this time period. We will also identify the rates of patient initiation of endocrine therapy. In addition, we will identify which specialties are most likely to initiate this discussion with the goal of identifying a clear referral route for optimal patient care. Differences will be evaluated using chi-square analysis.

Conclusions: The results from this study will help determine which providers are more likely to have a discussion regarding initiation of endocrine therapy for patients diagnosed with breast atypia or LCIS. Ultimately, with the goal of identifying a referral route for patients status post biopsy and increasing PCP prescriber rates by helping readily identify patients who would benefit from endocrine therapy.

Cost Comparison of Readmission vs Increased Inpatient Management for Postpartum Hypertensive Disease

Alexis Rudnik, MD, HO2

Advisor: Todd Lovgren, MD

Introduction: Hypertensive disorders of pregnancy commonly affect women in the postpartum period and are one of the leading causes of postpartum readmission. While evidence exists to guide blood pressure management during the antepartum and intrapartum period, there is no available data to guide postpartum management. Data from a recent study pending publication showed that patients on antihypertensives with a BP <140/90 mmHg in the 12 hours immediately prior to discharge were 3 fold less likely to be readmitted due to complications of hypertensive disease in the postpartum period, implying a change in management of these patients may be indicated with unknown impact on the cost of the care provided. Since readmission typically comes at significant personal and societal cost we sought to determine how a change in management may impact healthcare costs.

Objective: To compare the costs associated with readmission and those generated by a recently described change in management of postpartum hypertension that may result in reduced readmission.

Study Design: Retrospective cohort study looking at patient data from 2017-2020 at a single tertiary care center. To estimate costs of the change in care proposed, we will use the readmission rate for those discharged normotensive on antihypertensives as the goal readmission rate. Overall cost of readmissions will be determined using median cost of readmission x number of excess readmissions determined in the pending publication. This will then be compared to the additional costs of managed care; determined by evaluating costs of additional hospitalization and medications.

Results: By analyzing the excess admissions beyond our baseline readmission rate of those discharged normotensive on antihypertensives, we will identify those postpartum readmissions that could have potentially been prevented by more aggressive inpatient management. We will then use this data to perform cost comparisons of the readmissions vs the hypothetical costs of increased management, specifically including costs of extended inpatient stay prior to initial discharge and cost of 6 week course of long-acting antihypertensive prescriptions. This will be contrasted to those costs associated with an ER evaluation, readmission, or postpartum clinic blood pressure checks. The anticipated contrast in system-wide costs will determine the cost savings vs additional costs associated with the proposed change in postpartum blood pressure management.

Conclusions: We hope this study will affirm our expectation the cost of readmission exceeds that of proactive management of postpartum HTN. These findings would further encourage the adoption of this care strategy as it would not only improve quality of care but direct cost savings to the most expensive healthcare system in the world.

Postpartum depression among medical residents

Emma Bye, MD, HOIII OB/GYN, Rebecca Leval, MD HOIII Psychiatry
Advisors: Laura Cudzilo, MD, Jean Amoura, MD and Marley Doyle, MD

Introduction: Depression among medical residents across all medical specialties has been well documented over the course of the past ten years. Rigorous hours, stressful life transitions, and work family conflict have impacted depression among residents. A meta-analysis in 2015 of 17,560 residents estimated the rate of depression at 28.8% of all trainees. Physicians are at a significantly higher risk of depression as well as suicide compared to the general population. The rate of suicide among male physicians is 1.41 times higher and female physicians are 2.27 times higher than their counterparts in the general population. One transition that is central to work-family conflict that has not been well studied or quantified is the transition to parenthood while in residency. Postpartum depression among the general population is 11% for women and 8.4% for men. Studies have shown the greatest lifetime risk of depression for both women and men is in the first year after the birth of their child. The increased risk of the postpartum period coupled with the stressful demands of residency training may increase medical residents' rate of postpartum depression.

Objective: Evaluate and compare rate of maternal and paternal postpartum depression among residents to the general population. Identify areas to improve support for resident parents.

Study Design: We utilized a developed and piloted survey. They survey was distributed via anonymous survey on email link to both male and female medical residents of targeted specialties including OB/GYN, family medicine, internal medicine, pediatrics and psychiatry starting here at UNMC as well as Creighton University in hopes of further national distribution. The survey will also collect demographics, medical specialty, history of depression, year in residency during childbirth, support from residency program, NICU stay, and time off for family leave. This is a collaborative project with psychiatry. Together collected and contacted program coordinators from varying programs developing a listserv for survey distribution.

Results/Conclusions: Survey is currently in the distribution phase and data is being collected both for UNMC and Creighton residents. According to ACGME in 2017-2018 there are 135,326 U.S. residents within 11,214 programs with only a small portion of these being parents. This is a large population to sample; therefore collaborating with and sampling a portion of residents among varied specialties is currently the most realistic option. Determining the rate of postpartum depression among residents may provide insight on the scope of the problem. The open comment section of the survey will help identify areas of improvement for additional support for this at-risk population. Most importantly it is the hope that this study will help to decrease the stigma surrounding both maternal and paternal depression during residency. Limitations of the study include recall bias, potentially low response rate, and social desirability bias.

UNMC Treatment Success in Single Dose vs Two Dose Methotrexate for Ectopic Pregnancy

Carly Jennings, MD HO3
Advisor: Jean Amoura, MD

Introduction: An ectopic pregnancy is defined as a pregnancy that occurs outside of the uterus. Ectopic pregnancies account for approximately 2% of all pregnancies and 3-4% of pregnancy related deaths. Surgical and medical management may be offered in a hemodynamically stable patient. The mainstay of medical treatment is methotrexate which acts as a folate antagonist that binds to dihydrofolate reductase resulting in inhibition of cell division. This affects actively proliferating cells such as trophoblastic tissue. Currently, there are three methotrexate protocols for ectopic pregnancy that are widely accepted – a single dose, a two dose and a multidose protocol. A recent meta-analysis by Alur-Gupta et. al, demonstrated that treatment with two dose methotrexate was superior to the single dose methotrexate in treatment of ectopic pregnancies. This meta-analysis changed our practice at UNMC. Prior to October 2019, treatment of ectopic pregnancies included the single dose methotrexate treatment. After 2019, ectopic pregnancies are treated with the two-dose methotrexate treatment. At our institution there is a knowledge gap between success rate of the single dose vs two dose methotrexate treatment in ectopic pregnancies.
Objective: The aim of this study is to look at success rates, defined as beta-hCG <5 IU/L without surgerical after Methotrexate administration between the single dose and two dose treatments. Secondary aim is to evaluate the time it took for beta-hCG to get <5 IU/L between the single dose and two dose methotrexate treatments.
Results: I intend to analyze the success rate of single-dose treatment prior to October 2019 to two-dose Methotrexate after October 2019 in treatment of ectopic pregnancy and to evaluate the length of time each treatment required to achieve beta-hCG <5 IU/L. Success rate is defined as beta-hCG < 5 IU/L after Methotrexate administration without need for surgical intervention.
Conclusions: The significance to this study is to provide quality improvement data in the treatment of ectopic pregnancy after the adoption of two-dose methotrexate treatment in October of 2019.

Stage I Hypertension and Pregnancy: Scope of Disease and Pregnancy Outcomes

Dana Marsh, MD, HOIII; Amy Miller, MD; Kristian Menard, MS3
Advisor: Karen S. Carlson, MD

Introduction: Chronic hypertension in pregnancy is associated with increased maternal morbidity and mortality, and poorer neonatal outcomes. Recent changes made by the American College of Cardiology and the American Heart Association have lowered the threshold for diagnosing hypertension in nonpregnant adults. Stage I hypertension is now defined as 1) Systolic blood pressure of 130-139 mm Hg or 2) Diastolic blood pressure of 80-89 mm Hg. Initiation of pharmacologic therapy is now recommended for those with stage I hypertension and an additional risk factor (cardiovascular disease, type II diabetes mellitus, chronic kidney disease, age 65 or older, or an estimated 10-year risk of atherosclerotic cardiovascular disease of at least 10 percent). The effect that this change may have on the diagnosis of chronic hypertension in pregnant women is unknown. There is currently insufficient evidence to suggest a change in the management of pregnant women with stage I hypertension. Additionally, the potential implications for resource utilization, including antenatal surveillance, are unknown based on these new criteria.

Objective: The main objective of this study is to determine whether women with stage I hypertension have a higher than expected rate of preeclampsia. Secondary aims include defining the rate of other adverse pregnancy outcomes associated with stage I hypertension, rate determination of stage I hypertension among pregnant women, and to identify risk factors for preeclampsia within the cohort of women with stage I hypertension.

Study Design: This is a retrospective cohort study of the Nebraska Medicine pregnant population. The cohorts include women defined as normotensive and those with stage I hypertension prior to 20 weeks gestation. Study participants were identified retrospectively utilizing chart review of the 932 deliveries at Nebraska Medicine from 1/1/19 through 7/31/19 Inclusion criteria include women age 19 or older with singleton pregnancies who had at least two documented blood pressure readings between 8w0d and 19w6d gestation, and who delivered at Nebraska Medicine. 540 charts were selected for inclusion. The primary outcome is to compare rates of preeclampsia between normotensive women and women with stage I hypertension.

Results: The rates of stage I hypertension and chronic hypertension were 12.6% and 6.9%, respectively. Preeclampsia occurred in 19.1% of pregnant women with stage I hypertension, and in 8.8% of normotensive pregnant women. The significance is pending statistical analysis.

Conclusions: This study will provide information on how the changes in diagnostic criteria for hypertension impact pregnancy outcomes. This information will provide insight into the necessity for considering antenatal surveillance or pharmacologic therapy for pregnant women with stage I hypertension. This study will also highlight the scope of stage I hypertension among reproductive age women within the Nebraska Medicine health system.

A call for more holistic approaches: Physician mothers' responses to the lived experience of pregnancy loss

Taylar Swartz, DO MPH
Katherine Lessman, MD
Regina Idoate, PhD
Shannon Maloney, PhD

Objectives: To assess the experience of pregnancy loss and recovery among physician mothers in an effort to help guide health care provider's in delivering more holistic care, including better communication with and education of women experiencing pregnancy loss.

Methods: A cross-sectional mixed methods approach was conducted using a brief nine question social media-based survey of female physicians that had experienced a previous pregnancy loss. Quantitative data was collected from five close-ended questions to provide baseline demographic information, as well as categorical data. Two open-ended questions, asking 1) what was most surprising about the experience and 2) what should obstetricians and midwives know, were qualitatively analyzed by two independent investigators for emergent themes.

Results: A total of 1,379 participants completed the SurveyMonkey survey and common, overarching themes were identified. Respondents were reportedly most surprised by the emotional, social, intellectual and physical experiences of pregnancy loss. The most common emotional response experienced was grief with 91.3% selecting this response. Over one-third of women (33.1%) responded that it took over six months to emotionally heal from their pregnancy loss. The most commonly cited coping mechanism was discussing their experience with family and friends (60.87%), while only 12.84% found talking with their physician or midwife beneficial to their recovery. They wanted providers to know that pregnancy loss is experienced differently by everyone. Despite a small amount of physician mothers finding their healthcare provider helpful, respondents expressed gratitude for care providers and wanted to raise awareness of more holistic ways to support patients.

Conclusions for Practice: Based on the results of our survey, pregnancy loss is experienced differently by everyone; however, grief remains the most common emotional response. Many women do not see their physician or midwife as a helpful resource in the recovery process. The opportunity to provide better and more holistic care exists by addressing the emotional, environmental, intellectual, spiritual, physical, occupational, and social aspects of pregnancy loss and acknowledging that every woman's experience is unique.

Key words: Pregnancy loss, miscarriage, physician mothers' response, recovery, holistic

Significance: There is significant psychological morbidity associated with pregnancy loss and the recovery process is challenging. While pregnancy loss is prevalent, there are a range of experiences and emotions following the loss. The intensity of grief experienced by many, even when it is at an early gestation or a nonviable pregnancy, may not be adequately addressed by healthcare providers, leaving patients feeling a lack of support from the medical community. Due to their familiarity with the operational environment of medical settings, physician mothers who have faced pregnancy loss are uniquely positioned to provide insightful feedback surrounding the

recovery process. Gaining insight into their experience will help health care professionals provide better, more holistic care and understand the needs of their patients following pregnancy loss.

Evaluation of the Clinical Use of Antenatal Corticosteroids in Late Preterm Women at Risk for Preterm Delivery

Alissa Burchell, MD, HOIV

Advisor: Joshua Dahlke, MD

Objective: To determine if there is a temporal change in women who receive antenatal betamethasone (BMZ) before and after publication of a New England Journal of Medicine (NEJM) study recommending use in women at risk for delivering in the late preterm period.

Methods: This is a retrospective cohort study of women who underwent a delivery in the late preterm period (34 0/7 weeks – 36 6/7 weeks) at a private hospital affiliated with an academic residency program. Women were included in this study if they met the conclusion criteria of the original study published in the NEJM. Women were evaluated to determine if they received betamethasone for fetal lung maturity through retrospective chart review. The number of women who received BMZ before and after the NEJM study publication were compared using a Cochran-Armitage linear trend test.

Results: A total of 737 charts were reviewed. 366 women delivered before the NEJM publication and 371 delivered after its publication. Exclusions were made for women who had previously received BMZ, were diabetic and delivered multiple gestations. 466 women were analyzed. No significant differences in maternal demographic data were noted between the two groups. Mothers who delivered in the late preterm period after the NEJM study publication were found to be statistically more likely (6.9% vs 34.9%, (p-value < 0.00001)) than those who delivered prior to the study publication. Two women in this study group developed chorioamnionitis and two developed endometritis, both in the post-NEJM study period. One woman received steroids prior to admission and was subsequently diagnosed with chorioamnionitis during admission. The other three women did not receive steroids.

Conclusion: This publication of a landmark journal article, change to ACOG clinical practice guidelines as well as a meeting at the study-hospital resulted in a statistically significant change of practice within one year at a single site, residency-associated private hospital. Maternal development of chorioamnionitis or endometritis was a rare outcome in this study group and this study is not sufficiently powered to determine a statistical difference in those who did and did not receive betamethasone.

Title: The Impact of "Meds to Beds" on Postpartum Opioid Use

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OBJECTIVE: To determine if there is a difference between opioid prescriptions filled before and after the implementation of "Meds to Beds" in women undergoing cesarean delivery (CD) and to assess maternal, pregnancy and labor characteristics associated with filling opioid prescriptions.

METHODS: This is a retrospective cohort of women who underwent cesarean delivery (CD) from March 1, 2015 to December 31, 2015 and June 1, 2016 to December 31, 2016 at a single tertiary care center. Women were included if CD was performed at our Center and received an

opioid prescription within 6 days postpartum. By using chart review and pharmacy data, women that opted into "Meds to Beds" were identified. “Meds to Beds” is an institutional free service whereby all postpartum prescriptions are reviewed by a pharmacist one on one with the patient and filled at the bedside prior to discharge. Discharge Pharmacies were contacted to verify if opioids were dispensed in the pre-implementation group. The proportion of women who filled the opioid prescription before and after the implementation of “Meds to Beds” were then compared.

RESULTS: 484 patient charts (291 prior to “Meds to Beds” and 205 after) were reviewed for eligibility. After exclusions due to delivery at outside hospital, vaginal delivery, prior opioid use or insufficient pharmacy data, 225 women were analyzed (86 prior to “Meds to Beds” and 139 after). There were no significant maternal demographic differences between groups. Women who had none or 1 prior CD were more likely to fill their opioid prescription compared to women who had undergone 2 or more CDs. Regarding our primary outcome, a significant number of women were more likely to fill their opioid prescription after implementation of “Meds to Beds” (97% vs 81%, $p < 0.001$).

CONCLUSION: Implementation of “Meds to Beds” improved opioid fill rate among women undergoing CD and this model may provide a generalizable approach for peripartum opioid stewardship by optimizing postpartum prescription administration.

Introduction

Acute opioid use and subsequent chronic abuse as well as provider prescribing practices remains an important public health topic among clinicians. Media attention on the subject highlighting the growing opioid epidemic in the United States has increased awareness among prescribing physicians. According to the Center for Disease Control and Prevention (CDC), the rate of opioid overdose resulting in death increased fivefold between the years 1999 and 2001. Mack and colleagues reported, in 2013, more Americans were killed via drug overdose than motor vehicle accidents[7]. Visits to the Emergency Department for drug overdose have also increased over this time period. Among these visits, nearly 130 per 100,000 women were specifically for opioid pain reliever overdose[1]. Among women between the ages of 18 and 44, 1 percent of pregnant women and 2.3% of non-pregnant women report non-medical usage of opioids within the previous 30 days with a large majority reporting that a doctor was their source of opioid prescription[2]. These statistics demonstrate that opioid use and overuse should be a topic at the

forefront among medical professionals.

Notably, about 4,000,000 deliveries occur annually within the United States, making childbirth the most common reason for admission into the hospital[6]. Given the circumstances of labor and delivery, many women are first exposed to opioids during labor and the postpartum period. They are not only often managed intrapartum with opioid therapy, but are often discharged with a prescription for home use. Recent retrospective studies of this population demonstrated that 12% of women following vaginal delivery filled their opioid prescription within 5 days of delivery and an additional 14% filled a second prescription within 6-60 days following delivery. Other studies have shown approximately 1 in 300 opioid naïve women became persistent users after filling a prescription following cesarean delivery[4]. Tobacco use, mental health condition, and prior substance use disorder were among the top predictors for filling a script or becoming a chronic opioid user following delivery[5]. Between the years of 2004 and 2012, the state of Colorado identified 211 total maternal deaths within the first year of delivery. Of these, there was a death ratio of 5 per 100,000 live births that were due to overdose. On toxicology, 21 of the 63 women whose death was from self-harm were positive for pharmaceutical opioids[3]. In March of 2017, the CDC released a report evaluating chronic opioid use in opioid naïve, cancer-free adults who received their first prescription for opioids. This study found the largest predictors for chronic use were those patients that continued treatment for greater than 5 and 35 days. Additionally, patients that were given a second prescription or refill, prescriptions equal to 700 morphine milligrams, and any script with 10 and 30 day supplies. Approximately 1 in 7 people were using opioids 1 year later if given a refill or second prescription. Their study revealed a 6% probability of continued use at 1 year, and a 2.9% at 3 years[8]. Obstetricians and other physicians must be aware of the potential for opioid dependency particularly when prescribing opioids during the postpartum period.

On March 15, 2016 the pharmacy at The University of Nebraska Medical Center started a postpartum prescribing program called "Meds to Beds." This program dispenses medications, including opioids, directly to the patient prior to discharge home. All patients are contacted on admission to Labor and Delivery via telephone or in person encounter to discuss the option of enrolling in the program. If a patient chooses to enroll in this free service, she will receive counseling by a pharmacist or pharmacy staff as well as medication delivery to her hospital room prior to discharge. Prescriptions are transferred to home pharmacy of the patient’s choice after

discharge. Medications are charged to the patient's account and billed at a later time. A patient is able to decline all or some of the medications prescribed by the physician.

Objective

To determine if there is a difference between opioid prescriptions filled before and after the implementation of "Meds to Beds" in women undergoing cesarean delivery (CD) and to assess maternal, pregnancy and labor characteristics associated with filling opioid prescriptions.

Materials and Methods

"Meds to Beds" started on March 15, 2016 on Labor and Delivery at Nebraska Medicine. This study retrospectively evaluated opioid fill rates for women who delivered via cesarean section from March 1, 2015 to December 31, 2015 prior to the implementation of "Meds to Beds", and compared fill rates to women that delivered June 1, 2016 to December 31, 2016 following implementation. We allowed for a 3 month wash out period before and after implementation of the program. Women were excluded if they had chronic opioid use or opioid use during pregnancy. We assumed that the proportion of opioids filled prior to the program was 70% (as based on previous research) and that the proportion would increase by 20% to 84% among those women who used the "Meds to Beds" program. In order to have 80% power to detect this change, 141 women were needed in each study group. This study received expedited IRB approval. An analysis within the electronic medical record Epic was run to identify women who underwent cesarean delivery and received an opioid prescription within 6 days postpartum. Initially, 141 charts were obtained for each study group (before and after implementation). However, after collecting the data, unexpected barriers to obtaining opioid information were encountered. These barriers included: delivery at a sister institution that did not have the "Meds to Beds" program and pharmacy data could not be obtained from Walgreen's, HyVee and CVS prior to 2016. An additional 400 charts, 200 before and 200 after implementation of "Meds to Beds", were requested at that point in attempt to meet power.

Via chart review, characteristics were obtained and entered in to our secure database. Maternal characteristics of interest included: age, race, ethnicity, zip code, history of substance use (non-opioid), tobacco use, mental health condition, single vs multiple gestation, postpartum complications, parity, postpartum tubal ligations, postpartum dilation and curettage, number of prior cesarean section, need for additional procedures, labor time prior to cesarean, duration of rupture of membranes prior to delivery, history of physical or sexual abuse, breast or bottle feeding

and NICU admission. In collaboration with the UNMC pharmacy, women that opted into "Meds to Beds" were identified. Each patient's discharging pharmacy was recorded and then contacted to obtain opioid filling information.

Using Fisher's exact test and p-value of 0.05, the number of patients that filled their opioid prior to "Meds to Beds" were compared to those that filled their opioid following implementation of "Meds to Beds." Additionally, maternal and labor characteristics were compared between those women that in general filled their opioid, versus those that did not fill their opioid. Fisher's exact test was used to compare these variables between the 2 groups.

Results

484 total patient charts were reviewed for eligibility. 291 charts prior to "Meds to Beds" and 205 after "Meds to Beds" were reviewed. After exclusions (due to delivery at an outside hospital, vaginal delivery, prior opioid use or insufficient pharmacy data) a total of 225 women were analyzed. 86 charts prior to "Meds to Beds" and 139 charts after were included in the study (Chart 1). No maternal demographic differences were statistically significant between the two groups (Table 1). Regarding our primary outcome, a significant number of women were more likely to fill their opioid prescription after implementation of "Meds to Beds" (97% vs 81%, $p < 0.001$) (Table 2). It was found that women who had none or 1 prior CD were more likely to fill their opioid prescription compared to women who had undergone 2 or more CDs (Table 3).

Conclusions

This study demonstrates that "Meds to Beds" significantly improved opioid prescription fill rates in women undergoing cesarean delivery at our institution. Our study differed from prior studies suggesting that tobacco use, mental health condition, and prior substance use disorder increased likelihood of filling opioid. We found that number of cesarean sections was the only predictive factor for filling opioid prescription. A strength of this study is that there was a period of time (the study window) of which no other intervention occurred to impact out study results. We had a set date of implementation and were able to use this as a transition time frame. Additionally, allotted a wash out period for the implementation to occur. One limitation of this study included the barrier to obtaining pharmacy data from major retail pharmacies prior to 2016 and thus study size prior to implementation of "Meds to Beds" was not ideal. With this being a retrospective study there is risk of inherent bias. This model may provide a generalizable approach for other institutions who desire to maximize peripartum opioid stewardship by optimizing postpartum prescription

administration. Further research could be done to specifically look at prescribing habits between physicians at a single institution or group of practice. Future studies could demonstrate similar benefit for other commonly prescribed medications in the postpartum period using "Meds to Beds".

Table(s) or chart(s)

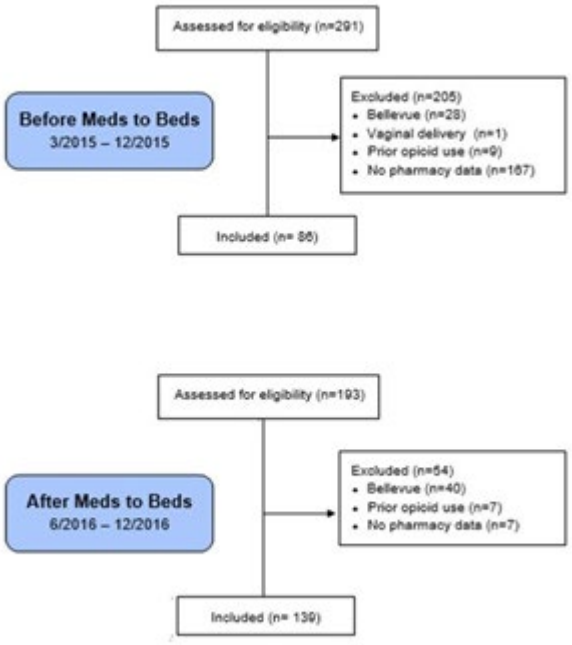

Chart 1. Study Group Exclusion and Inclusion

	Before Meds-to-Beds	After Meds-to-Beds	Significance
	n (%)	n (%)	
Age (years)	30.0 (5.3)	29.3 (5.6)	NS
Race/Ethnicity Non-Hispanic White Non-Hispanic Black Hispanic	 55 (65) 10 (12) 12 (14)	 88 (64) 25 (18) 15 (11)	NS

Other	7 (8)	9 (7)	
Non-Opioid Substance Use	9 (10)	11 (8)	NS
Tobacco Use Current Former Never	 13 (15) 18 (21) 55 (64)	 18 (13) 26 (19) 95 (68)	NS
Mental Health Condition	29 (34)	42 (30)	NS
Abuse	6 (7)	7 (5)	NS
Parity	2.5 (1.5)	2.8 (1.9)	NS
# of prior Cesareans 0 1 2 3 5	 47 (55) 19 (22) 14 (16) 4 (5) 2 (2)	 81 (58) 32 (23) 19 (14) 7 (5) 0 (0)	NS

Table 1. Demographics by “Meds to Beds” Timing

	Before Meds-to-Beds		After Meds-to-Beds		p-value
	N	n (%)	N	n (%)	
Filled First Opioid Prescription	86	70 (81)	139	135 (97)	<0.001

Table 2. Opioid Related Outcomes by “Meds-to-Beds" Timing

	Did Not Fill Opioid	Filled Opioid	Significance
	n (%)	n (%)	
Age (years)	31 (5)	29 (5)	NS
Race/Ethnicity Non-Hispanic White	 14 (70)	 129 (64)	 NS
Non-Opioid Substance Use	1 (5)	19 (9)	NS
Tobacco Use Current Former Never	 15 (75) 3 (15)	 135 (66) 28 (14)	NS

	2 (10)	42 (20)	
Mental Health Condition	9 (45)	62 (30)	NS
Abuse	0 (0)	13 (6)	NS
# of prior Cesarean Sections 0 1 2 3 5	 10 (50) 3 (15) 5 (25) 0 (0) 2 (10)	 118 (58) 48 (23) 28 (14) 11 (5) 0 (0)	0.011[c]
NICU Admission	7(35)	66(32)	NS
Tubal Ligation	6 (30)	31 (15)	NS
D&C	0	3 (1)	NS
Other procedures	0	17 (8)	NS
Gestations One	 19 (95)	 188(92)	NS
Postpartum Complications	1 (5)	34 (17)	NS
Newborn Feeding Breast	 15 (75)	 162 (79)	NS
Prior Labor Time No Labor <24 Hours 24-48 Hours >48 Hours	 12 (60) 4 (20) 3 (15) 1 (5)	 122 (60) 52 (25) 28 (14) 3 (1)	NS
Duration of ROM No Rupture <24 Hours 24-48 Hours >48 Hours	 10 (50) 8 (40) 1 (5) 1 (5)	 130 (63) 63 (31) 7 (3) 5 (2)	NS

Table 3. Procedure Related Measures by opioid prescription filled or unfilled

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How low is too low? Postwash Total Motile Sperm Count Effect on Pregnancy Outcomes in Intrauterine Insemination

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Abstract

Intrauterine insemination (IUI) is a frequently used method to treat couples with infertility. The aim of this study was to determine a minimum threshold of TMSC on semen analysis to offer IUI cycles. This is a retrospective cohort study of all IUI cycles at a private practice infertility center from June 2014 to May 2018. Our primary outcome of interest was the presence or absence of clinical pregnancy after each cycle. Clinical pregnancy was defined as fetal cardiac activity on ultrasound. A total of 999 women underwent 2169 IUI cycles. The overall clinical pregnancy rate was 19.8% per cycle. During the first IUI each woman underwent, there was an increase in clinical pregnancy with increasing TMSC, OR 0.44 for TMSC ≤1M, 0.56 for TMSC 2-5M, and 0.99 for TMSC 6-10M, compared to TMSC >10M with p-values of 0.27, 0.057 and 0.975 respectively. Among all IUI with TMSC 6-10M, pregnancy outcomes improved with morphology >4% OR 0.84, compared to morphology <4% OR 0.25, both relative to TMSC >10M. Using receiver operating characteristic curves, we did not identify a TMSC threshold to offer IUI, although there was a positive correlation between TMSC and IUI success.

Keywords: Intrauterine insemination, total motile sperm count, male infertility, female infertility, total motile sperm count

Introduction

Infertility is defined as the inability for a couple to achieve a successful pregnancy after at least 12 months of regular, unprotected sexual intercourse. Treatment can be initiated after 12 months in women under 35 years old and after 6 months in women 35 or older. (Definitions of infertility, 2020). Estimates of the incidence of infertility range from 8-24% of couples (Borght & Wyns 2018, Mankus et al., 2019, Thorma et al., 2013). A recent study estimated the prevalence of

infertility in the United States to be as high as 15.5% among all reproductive aged women and 24.3% among nulliparous women. (Thorma et al., 2013). There are many factors that contribute to a couple's ability to conceive including the woman's age, anatomy of the uterus, ovulatory factors, and semen parameters. Males are the sole factor in approximately 20-30% of infertile couples and contribute to about 50% of all cases of infertility (Borght & Wyns, 2018, Mankus et al., 2019). Intrauterine insemination (IUI) is a frequently used method to treat couples with infertility for a variety of etiologies and is often utilized prior to proceeding with artificial reproductive technology (ART).

The World Health Organization has published reference values for normal semen analysis parameters but these do not correlate with infertility (Mankus et al., 2019). The total motile sperm count (TMSC) has been associated with the success of IUI (Van Der Westerlaken et al., 1998). TMSC is calculated by multiplying volume, concentration, and motility. There is evidence of decreased pregnancy rates with TMSC less than 5 and 10 million (VanVoorhis, et al., 2001, Merviel et al., 2010, Miller et al., 2002), yet there has been efficacy of reported IUI success with TMSC under 1 million (Merviel et al, 2010). As such, there remains to be a consensus on semen parameters for which to recommend IUI in the infertile population. Further defining TMSC and associated pregnancy rates allows for more precise patient counseling and may also delineate a clearer threshold for escalation of care to in vitro fertilization. This may decrease the time to pregnancy and the financial burden of offering infertility treatment that is less likely to be effective. The aim of this study was to determine a minimum threshold of TMSC on semen analysis to offer IUI cycles.

Material and Methods

This is a retrospective cohort study of all IUI cycles at an academic affiliated, private practice infertility center from June 2014 to May 2018. After Institutional Review Board approval, we obtained female characteristics including age, gravida, parity, BMI, AMH, AFC, tubal patency,

stimulation medications, number of dominant follicles, and endometrial thickness. Natural cycle, clomiphene, letrozole, and gonadotropins were used at the discretion of the provider. All patient's had known, or suspected tubal patency based on hysterosalpingogram, chromopertubation at the time of laparoscopy, or recent pregnancy. Three cycles were excluded from the final analysis as the insemination was completed intravaginally due to patient discomfort with speculum exams.

Follicle number and size were monitored by ultrasound. The frequency of follicular monitoring was also completed at the discretion of the provider. The use of ovulation trigger was documented. Semen samples were collected on the day of insemination after a suggested 2 days of ejaculatory abstinence. Semen was processed with a density gradient centrifugation process for both fresh and frozen sperm. The following semen parameters were collected: post wash TMSC, concentration, motility, and wet mount morphology. Wet mount morphology was based on the 4th edition World Health Organization semen analysis guidelines. IUI was timed for approximately 36 hours following the trigger.

Insemination was performed using a sterile catheter with the patient in dorsal lithotomy. The patient remained supine for at least 10 minutes following the insemination. Luteal phase support, in the form of vaginal progesterone, was initiated 4 days after hCG triggered ovulation. Home pregnancy test was performed 14 days following the insemination. Our primary outcome of interest was the presence or absence of clinical pregnancy, defined as fetal cardiac activity on ultrasound, after each cycle. Serum pregnancy, defined as an elevated beta HCG, was also collected. However, we felt clinical pregnancy describes a more meaningful benchmark of pregnancy. Ultrasound following positive pregnancy test was completed at 8 to 9 weeks following insemination.

Statistical analyses were performed using STATA v16.1 (StataCorp LLC, College Station, TX). software. Data are presented using means and standard deviations (SD) or ranges for continuous measures and frequencies and percentages for categorical measures. Different cycles from the

same woman were not independent, thus different methods were used to evaluate results from the first IUI from each woman and all IUI cycles. For analysis of first IUI, simple logistic regression models were used to evaluate each measure's association with clinical pregnancy, while mixed-effects logistic regression models with a random effect for each subject were used in a similar capacity for all IUI cycles. Measures from the simple models with significance of $P<0.10$ were included in multivariable models for clinical pregnancy. Results from all of these models are presented as odds ratios with 95% confidence intervals. Similar models were also used for a secondary analysis of associations of other measures with clinical pregnancy within subsets of patients based on their level of morphology using a cut point of 4%. A receiver operating characteristic (ROC) curve was used to evaluate whether there was a specific cut point in TMSC where the likelihood of clinical pregnancy increased substantially.

Results

A total of 999 women underwent 2169 IUI cycles during this four-year period. The population included women aged 21 to 47 with an average age of 32.1 at the time of their first IUI. 54% of the women had never conceived a pregnancy. The average male age was 34.6 with a SD of 5.1. The average couple underwent 2.17 IUIs with a range of 1-9. BMI ranged from 16.8 to 53.2 with an average BMI of 28.8.

3.6% of all IUI cycles were natural cycle, while 10.4% were treated with clomiphene, 28.6% with letrozole, 12.1% received gonadotropins, and 45.3% received a combination of clomiphene or letrozole with gonadotropins. HCG was given to initiate ovulation in 2139 cycles while lupron was used in four cycles. An ovulation induction agent was used in all but 9 cycles. The average peak estradiol reached 351 in those who obtained a clinical pregnancy.

The overall clinical pregnancy rate was 19.8% per cycle while pregnancy rate of only the first IUI per patient was 19.2%. The overall clinical pregnancy rate per couple was 40.2%. There were 39 multifetal gestations, 9.1% of all clinical pregnancies. During the first IUI each couple underwent,

there was an increase in clinical pregnancy with increasing TMSC, OR 0.44 for TMSC ≤1M, 0.56 for TMSC 2-5M, and 0.99 for TMSC 6-10M, compared to TMSC >10M with p-values of 0.270, 0.057 and 0.975 respectively. For all IUI cycles, there was also an increase in clinical pregnancy with increasing TMSC, OR 0.57 for TMSC ≤1M, OR 0.57 and for TMSC 2-5M, and 0.83 for TMSC 6-10M, compared to TMSC >10M with p-values of 0.230, 0.010 and 0.298 respectively (Table 1). S Serum pregnancy results followed a similar trend with increasing serum pregnancy with increasing TMSC: OR 0.33 for TMSC ≤1M, 0.62 for TMSC 2-5M, and 0.80 for TMSC 6-10M, compared to TMSC >10M with p-values of 0.142, 0.078 and 0.340, respectively for first IUI cycles and OR 0.43 for TMSC ≤1M, 0.58 for TMSC 2-5M, and 0.84 for TMSC 6-10M, compared to TMSC >10M with p-values of 0.079, 0.009 and 0.310, respectively for all IUI cycles.. Multivariable regression was used to evaluate these associations in the presence of confounding factors to clinical pregnancy. With the exception of age and number of dominant follicles, no other significant contributing factors were identified. In secondary analysis using subsets of patients based on morphology, clinical pregnancy outcomes improved substantially with morphology ≥4% compared to morphology <4%. The percentage of cases resulting in clinical pregnancy increased from 5% to 8% for those with TMSC ≤1M, from 0% to 7% for those with TMSC 2-5M, from 6% to 23% for those with TMSC 6-10M, and from 16% to 26% for those with TMSC >10M (Table 2).

Using the receiver operating characteristic curve, we did not identify a TMSC threshold to offer IUI, although there was a positive association between TMSC and likelihood of clinical pregnancy with area under the curve 0.5578 (Figure 1). No pregnancies were obtained after 6 IUI cycles in each couple, consistent with prior studies (Merviel). The lowest TMSC resulting in pregnancy was 660,000.

Discussion

Intrauterine insemination is a commonly utilized treatment for couples who present with infertility. Appropriate patient selection for intrauterine insemination therapy is very important in order to decrease time to pregnancy as well as to provide more cost effective care.

Our study is a retrospective cohort study at a single infertility practice looking at all IUI cycles over a 4-year period. In our study, a clinical pregnancy was almost twice as likely when TMSC >5 million, consistent with Merviel et al. A gradual decline of clinical pregnancy is present with TMSC under 5 million. Additionally, when TMSC <5 million, there was a substantial improvement in pregnancy outcomes with wet mount morphology ≥4%.

Over the 4 years of data, we were able to obtain a large sample size. Providers at the clinic were stable and no changes to semen processing were made over the study period. There are inherent limitations of a retrospective cohort study design. The population was heterogeneous and made up of patients with a variety of infertility diagnoses including unexplained infertility, endometriosis, and male factor. Same sex couples were also included in this study. When donor sperm cycles were removed, the data followed a similar trend of increased clinical pregnancy rate with increased TMSC (data not shown). Certainly the final goal of a couple struggling with infertility is to have a live birth. While this study evaluates clinical pregnancy rate, there was not complete data available regarding live birth rate. Despite smaller odds ratios for the TMSC <1 million group, these results were not significant, a result of the small size of this group (only 20 women with a total of 44 cycles). Certainly having a larger sample of this particular cohort could help to better identify thresholds of TMSC for which to offer IUI to an infertile couple.

Although no distinct threshold of TMSC was identified to offer IUI versus proceeding with ART, there is a positive correlation between TMSC and IUI success. There appears to be improved outcomes with TMSC >5M compared to lower levels. Well-defined pregnancy rates based on semen parameters will allow for more personalized and direct counseling of infertility patients and also allow for more targeted therapy recommendations based on pregnancy success rates. Further

research is needed to further delineate semen parameters for which to recommend certain treatment for infertility patients. A follow up study, using a larger sample size, particularly in the lower TMSC ranges, is necessary to further characterize the upper limits of efficacy of IUI specimens.

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44	6 (14)	0.57	0.230	20	2 (10)	0.44	0.270
218	30 (14)	0.57	0.010	105	13 (12)	0.56	0.057
279	51 (18)	0.83	0.298	119	24 (20)	0.99	0.975
1627	343 (21)	Ref.	Ref.	754	153 (20)	Ref.	Ref.

Table 1. Clinical pregnancy rate based on total motile sperm counts in all IUI cycles and only the first IUI per couple.

21	1 (5)	0.18	0.230	12	1 (8)	0.24	0.202
32	0 (0)	N/A	N/A	74	5 (7)	0.17	<0.001
36	2 (6)	0.25	0.158	109	25 (23)	0.84	0.518
119	19 (16)	Ref.	Ref.	1368	349 (26)	Ref.	Ref.

Table 2. Clinical pregnancy rate based on total motile sperm counts in IUI samples with morphology <4% and morphology ≥ 4%.

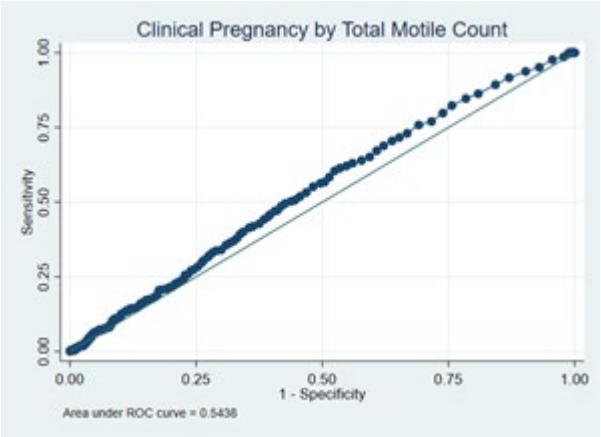

Figure 1. Receiver operating characteristic curve for post-wash total motile sperm count in predicting clinical pregnancy. The x-axis represents 1-specificity and the y-axis represents sensitivity.

DOES GnRH DOWN REGULATION AMONGST WOMEN WITH ABNORMAL BCL6 AND/OR BETA 3 INTEGRIN EXPRESSION IMPROVE IMPLANTATION RATES? AN INTERIM ANALYSIS.

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OBJECTIVE:
Does GnRH agonist treatment in patients with abnormal expression of BCL6 and/or beta 3 integrin restore implantation rates to a comparative level with those patients without known endometrial receptivity abnormalities?

DESIGN:
A single-institutional, retrospective convenience cohort analysis of 44 patients with recurrent implantation failure was performed comparing patients with abnormal expression of BCL6 and/or beta 3 integrin treated to GnRH agonist therapy versus 39 patients with tubal factor infertility in 2019.

MATERIALS AND METHODS:
Patients were identified using CPT diagnostic/billing codes. A manual review of electronic medical records was used to screen for patients that met the inclusion criteria. PC SAS version 9.4 was used for analyses. The statistical level of significance was set to 0.05. The nonparametric Mann- Whitney test was used to compare GnRH agonist versus tubal factor for continuous variables. Fisher's exact tests were used to make comparisons on categorical variables.

RESULTS:
After accounting for age, BMI, gravity, parity (p-values of 0.72, 0.59, 0.94, and 0.74 respectively) the only significant descriptive characteristic identified was prior ART (0.003) skewed towards prior treatment in those patients with recurrent implantation failure. Of the 44 patients identified to have recurrent implantation failure, 25 underwent GnRH agonist therapy and subsequent embryo transfer. Of these patients, 21 had successful implantation defined as a positive beta-HCG. Thirty- nine patients were identified to have tubal factor infertility. Within this cohort, 15 underwent embryo transfer resulting in 12 successful implantations.

CONCLUSIONS:
Endometriosis affects 20-40% of women with infertility and is known to decrease fecundity by approximately 50%. There is a high correlation between elevations of BCL6 and inadequate secretion of beta 3 integrin and a concurrent diagnosis of endometriosis. Further, research has shown that patients with abnormal BCL6 and beta 3 integrin expression have approximately an 18% pregnancy rate in their next transfer attempt versus 70% pregnancy rate in those patients with normal expression.

Our preliminary data suggests that GnRH agonist treatment in patients with abnormal expression of BCL6 and/or beta 3 integrin restores implantation rates to a comparative level with those patients without known endometrial receptivity abnormalities.

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