The Transgender Patient and Perioperative Complications

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DNAP 893a: Evidence Based Practice Va: Dissemination

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March 15, 2024

Abstract

There are an estimated 1.4 million adults in the United States that currently identify as transgender. As the social acceptance of the transgender population continues to increase, it is expected that this number will continue to rise. There are a reported 61% of transgender individuals who have pharmaceutically transitioned with Hormone Replacement Therapy and 25% having undergone Gender Affirming Surgery. As health insurance coverage encompasses treatment options and surgical services for this population, anesthesia providers must be aware of potential perioperative complications. Potential risks include cardiovascular complications, altered respiratory physiology, and distorted airway anatomy. Currently, there is a gap in knowledge in the care of transgender patients among anesthesia providers as well as a lack of a standardized curriculum in anesthesia education addressing transgender patients during the perioperative period and related anesthetic considerations. Therefore, a continuing education (CE) module via the Echelon platform was created to reduce the gap in knowledge among anesthesia providers related to the care of the transgender population in the perioperative setting.

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The Transgender Patient and Perioperative Complications

Transgender patients pose a unique set of challenges to the certified registered nurse anesthetist (CRNA). This patient population is often on hormone replacement therapy (HRT) or has undergone gender affirming surgery (GAS) and gender confirming practices, altering both the body's biological anatomy and physiology, which can potentiate unanticipated perioperative complications (Leinung & Joseph, 2020; Nolan et al., 2021). Currently, CRNAs lack training and education of how the therapies the transgender population undergo affect the perioperative course and the best approach to their anesthetic management (Hatfield, 2017).

Significance & Background of Clinical Problem

There are an estimated 1.4 million adults in the United States that currently identify as transgender (Flores et al., 2016). As the social acceptance of the transgender population continues to increase, this number is expected to rise. Furthermore, as health insurance coverage broadens to encompass gender affirming care, it is more affordable for this patient population to seek surgical services, which will increase their presence in the operating room (Canner et al., 2018). Considering that a reported 61% of transgender individuals have pharmaceutically transitioned with HRT and 25% having undergone GAS, CRNAs must be prepared to recognize and address these essential differences to limit potential perioperative complications for the transgender patient (James et al., 2016).

There are a variety of potential surgery-related complications that can occur among the transgender patient population undergoing certain treatment modalities, such as HRT and GAS. In the general surgical population, hormone therapy has put patients at an increased risk of surgical complications, especially from venous thromboembolism (VTE) (Chalhouh et al., 2008; Lee et al., 2015; Streed et al., 2017). The development of post-surgical VTE is associated with a

mortality risk of 13% (Al-hameed et al, 2017). Patients on HRT are also at an increased risk for cardiovascular disease and intraoperative cardiovascular events such as myocardial infarction (MI) and cerebrovascular accident (CVA). In the general patient population, mortality following cardiovascular events is 15-25%, and a nonfatal MI is a strong predictive risk factor for death within the next six months of the procedure (Devereaux, et al., 2005; Sazgary, et al., 2020). Although current research is lacking in the transgender population specifically, it is reasonable to conclude that transgender individuals receiving HRT are also at an increased risk for VTE and cardiovascular events during the surgical period.

Additionally, chest binding practices done by transgender males may lead to restrictive lung pattern of breathing. Without a tailor anesthetic plan, there is potential for perioperative pulmonary complications. Mortality is increased in patients who develop a postoperative pulmonary complication with 14-30% dying within 30 days of a major surgery compared to 0.2-3% without a postoperative pulmonary complication (Miskovic & Lumb, 2017).

In addition to HRT and chest binding practices, many transgender individuals undergo GAS, including surgical procedures altering the airway. These surgical changes can further potentiate the likelihood of a difficult airway situation which is a particular concern as airway difficulties account for 25% of anesthesia related deaths (Cook & MacDougall-Davis, 2012). Thus, provider awareness of these topics is essential to safe care (Mani et al., 2021; Johnston & Shearer, 2017).

Currently, there is a lack of evidence-based curriculum within nurse anesthetist education devoted to the safe and comprehensive perioperative care of transgender patients. Therefore, to provide higher quality patient care, the investigators of this scholarly project created a learning module that presents CRNAs with potential perioperative complications that may occur in

transgender patients that are currently receiving HRT, those who undergo chest binding practices or those who have had GAS.

PICOT Evidence Review Questions

Two PICOT questions were used to guide this review. The first question addresses the clinical problem: Are transgender patients (P) who have undergone hormone therapy or gender-affirming procedures and practices (I) at risk for perioperative complications (O)? The second question focuses on the innovation: For practicing anesthesia providers (P), does an educational need exist regarding the perioperative complications for transgender patients on hormone therapy or having received gender-affirming procedures and practices (I), and will an online module regarding this topic receive continuing education (CE) credit by the American Association of Nurse Anesthetists (O) by Spring 2023 (T)?

Search Strategies

Databases searched include: PubMed, Google Scholar, CINAHL, and ScienceDirect. Key search terms included: *transgender, transsexual, surgery, gender-confirming, gender-affirming, hormone, hormone therapy, estrogen, testosterone*, *venous thromboembolism, anesthesia, perioperative complications, airway complications* and *gap analysis*. MeSH terms included: *transgender persons* and *postoperative complications*. The limit was the English language. There were 240 articles identified. After reviewing the titles and abstracts for relevancy, 78 articles were selected, and 12 met inclusion criteria. Inclusion criteria included transgender, transgender therapy, gender-affirming surgery, perioperative complications, and within the last 5 years. Two case studies, three retrospective studies, one survey, four systematic reviews, and two gap analysis were included in the final count of 12 articles.

GRADE Criteria

The strength of the available literature was determined using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) criteria. An initial GRADE of 3 was assigned as the majority of articles were systematic reviews. The literature was then rated down due to imprecision resulting from small sample size. There was a lack of consistency of the independent variable which was the type of hormone treatment the patients were receiving. No criteria were met for grading up. In summary, a final GRADE of 2 was given. With the available current evidence, clinicians should be aware of the potential complications of hormone therapy and airway management in the transgender patient population.

Literature Review & Synthesis of Evidence

Although there are numerous possible perioperative complications that may affect the surgical outcome of transgender patients, this review will focus on the challenges that are critical to the anesthesia provider. The risks that are most prevalent in the literature are the potential for cardiovascular complications as a result of HRT, medication interactions with HRT, chest binding practices, altering respiratory physiology, and the effects of GAS on the airway anatomy. These complications can result in hemodynamic and airway compromise that the anesthesia provider must be able to anticipate and manage in order to provide a safe perioperative course.

Risk of Venous Thromboembolism

Minimal studies have been conducted to directly examine the effects of HRT on transgender patients. Though VTE is a well-known risk of estrogen therapy, findings suggest that its impact on transgender patients undergoing HRT is not fully established (Gaither et al., 2018; Kozato et al., 2021; Lawrence, 2006; Nolan et al., 2021). Therefore, information is drawn from the available data in cisgender individuals receiving hormone therapy in the form of birth control or postmenopausal replacement.

In the cisgender population, the use of systemic HRT is associated with an increased risk for the development of VTE, most notably in individuals taking an estrogen hormone therapy (Bergendal et al., 2016; Chalhoub et al., 2008; Lee et al., 2015; Streed et al., 2017). Estrogen HRT creates a hypercoagulable state, potentiating development of VTE and pulmonary emboli (PE). Estrogen hormone therapy is the most common HRT prescribed for male-to-female (MTF) transgender individuals (Boskey et al., 2019; Gaither et al., 2018; Kotamarti et al., 2021; Nolan & Cheung, 2020). This results in MTF transgender surgical patients on estrogen HRT having a higher incidence report of perioperative VTE and PE, thus increasing patient morbidity (Boskey et al., 2019; Chan et al., 2014).

It is prudent that the anesthesia provider is aware of the patient's prescribed hormone therapy to develop an anesthesia plan that places preventative measures on the development of VTE and PE. Prophylactic measures such as anticoagulation and sequential compression devices may be indicated in this patient population (Dalton et al., 2018; Chan et al. 2014). Additionally, the well prepared anesthesia provider will be vigilant in monitoring for and detecting changes in hemodynamic signs associated with these thromboembolic events such as hypoxemia, tachycardia, hypotension, and a decrease in end tidal CO2 are signs (Desciak & Marin, 2011). In the event the anesthesia provider suspects a PE, management should focus on stabilizing the patient by improving right ventricle function with positive inotropes and pulmonary vasodilators such as inhaled nitric oxide and maintaining blood pressure and cerebral perfusion pressure with vasopressor of choice. Administration of an anticoagulant is an appropriate initial therapy (Desciak & Marin, 2011).

Due to the cisgender population studies associating HRT with surgical VTE, HRT in transgender patients is commonly discontinued for a period prior to surgery (Boskey et al., 2019;

Gaither et al., 2018; Haveles et al., 2021; Nolan & Cheung, 2020). However, this data largely came from ethinyl estradiol administration, which is no longer recommended or commonly used for transition therapy (Gaither et al., 2018; Nolan & Cheung, 2020). The World Professional Association for Transgender Health and the Endocrine Society created transgender-specific guidelines to be utilized when caring for transgender patients on HRT; however, the data is based on extrapolations from the cisgender population, remains inconsistent, and is rarely based on evidence-based guidelines (Boskey et al., 2019; Haveles et al., 2022; Unger, 2016). While there is a lack of conclusive evidence that supports HRT cessation resulting in VTE risk reduction, there is evidence that stopping HRT in the perioperative period may potentially lead to psychological distress and poor physiological responses due to the sudden drop in estrogen levels (Casmiro & Cohen, 2019; Haveles et al., 2021; Kozato et al., 2021). Abrupt discontinuation of HRT leads to symptoms of withdrawal such as hot flashes, peripheral vasodilation, intense sweating, depressed mood, irritability, and anxiety (Boskey et al., 2019; Gaither et al., 2018; Lawrence, 2006; Nolan & Cheung, 2020). The anesthesia provider must be aware of these potential symptoms as they mirror anesthetic related complications such as postoperative delirium and NPO induced hypoglycemia (Kain et al., 2021).

If the risk for VTE is low and proper prophylaxis is employed, it may be unnecessary to stop HRT during the perioperative period (Gaither et al., 2018; Lawrence, 2006; Nolan et al., 2021). HRT management during the perioperative period should be individualized based on patient-specific risk factors for the development of VTE such as obesity, lengthy surgical procedures and recovery time, increasing age, and the use of estrogens (Anderson & Spencer, 2003; Boskey et al., 2019; Kotamarti et al., 2021).

Risk of Cardiovascular Complications

Cardiovascular disease and cardiovascular complications are important considerations regarding transgender adults receiving HRT. Transgender women undergoing HRT experienced twice as many instances of myocardial infarctions (MI), coronary heart disease, and strokes compared to cisgender women over time (Alzahrani et al., 2019; Tollinche et al, 2020; Wierckx et al., 2013). Transgender men, however, experienced the same rates of cardiovascular disease and MI compared to cisgender individuals, even though HRT for transgender men increases cardiovascular risk factors such as elevated blood pressure, dyslipidemia, and impaired insulin sensitivity (Alzahrani et al., 2019; Tollinche et al., 2020; Wierckx et al., 2013).

Studies show that cisgender men with testosterone deficiency receiving testosterone therapy show higher rates of cardiovascular mortality (Durta et al., 2019; Tollinche et al., 2020). It is reasonable, therefore, to conclude that transgender men receiving testosterone therapy are at higher risk for cardiovascular events even though evidence is lacking regarding their morbidity and mortality. Therefore, all transgender individuals in the perioperative setting should be evaluated for surgical risk related to hormone therapy.

Preoperative considerations involve a baseline cardiac evaluation in those transgender men and women receiving hormone replacement therapy. Appropriate preoperative evaluation includes inquiring about the use of HRT, duration of therapy, cardiovascular symptoms such as chest pain or dyspnea, history of cardiovascular disease, risk factors for cardiovascular disease (obesity, hyperlipidemia or hypertension), and a physical examination. The Risk Assessment used to evaluate these components are validated tools completed by the primary care physician. The current recommendation is to use the revised cardiac risk index, also known as the Lee index, or the American College of Surgeons surgical risk calculator (Cohn & Fleisher, 2021).

The transgender individuals undergoing HRT are at increased risk for cardiovascular

events and cardiovascular disease. Though the evidence is lacking on anesthetic recommendations for this population, it is prudent for the anesthetic approach to resemble that of a patient with ischemic cardiac disease. Intraoperative anesthetic goals include prevention of ischemia by avoiding tachycardia, maintaining a blood pressure within 20% of baseline, and monitoring for myocardial ischemia (most commonly through ECG, with leads II and V5 having a sensitivity of 80%). These goals also apply for induction. A reasonable approach is to avoid tachycardia during laryngoscopy by using esmolol or fentanyl with induction, use of propofol 1 mg/kg or co-administration of phenylephrine 40-100 mcg with induction drugs (Hensely & Hogue, 2022).

Medication Considerations and Interactions related to HRT

In addition to HRT, transgender women may be prescribed anti-androgens. Anti-androgens facilitate a decrease in testosterone levels, resulting in feminization in the form of decreased body hair, a redistribution of fat, and breast growth (Boskey et al., 2019; Evered etal., 2020). In combination with HRT, the anti-androgens most commonly prescribed to the transgender female include spironolactone, bicalutamide, and cyproterone. (den Heijer & Tangpricha, 2017; Evered et al., 2020). Antiandrogens contribute to other possible perioperative complications oof the transgender surgical patient.

Spironolactone is an aldosterone antagonist that produces moderate anti-adrenergic activity and affects sodium and potassium exchange in the distal convoluted tubule on the nephron (Boskey, 2019; Gaither et al., 2018). As a result, spironolactone has potassium sparing diuretic properties; therefore, transgender female taking spironolactone may potentially experience hypotension electrolyte disturbances during the perioperative period (Boskey et a., 2019). The potassium sparing properties of spironolactone place the patient at risk for the

development of hyperkalemia, with risk being highest in patients with comorbidities such as hypertension, diabetes, and kidney disease. While the risk of life-threatening hyperkalemia is low in a healthy transgender patient on spironolactone, current guidelines recommend that patients on routine administration of potassium sparing diuretics should obtain serum potassium monitoring prior to surgery (Boskey et al., 2019; Hayes et al., 2022). In addition to hyperkalemia, spironolactone's diuretic properties can result in hypovolemia and hypotension during the administration of anesthesia (Boskey et al., 2019; Prior et al; 1989). The continuation of spironolactone during the perioperative period is patient specific and based on individual risk factors (Boskey et al., 2019; Evered et al., 2020).

The anti-androgens bicalutamide and cyproterone have anesthetic considerations concerning the liver (Boskey et al., 2019; Evered et al., 2020). Both bicalutamide and cyproterone have been found to cause drug-induced liver failure; thus, posing anesthetic risks (Bjornsdottir et al, 2018; Kumar et al. 2022). Numerous medications used during the perioperative period, including muscle relaxants and analgesics, depend on a healthy liver for hepatic metabolism. Although the risk of bicalutamide or cyproterone-induced liver injury is low, the anesthesia provider must consider this complication when forming the anesthetic plan (Bjornsdottir et al, 2018; Kumar et al. 2022). In the case the transgender female has developed liver injury, the anesthesia provider must be vigilant in avoiding the administration of medications that may further contribute to liver injury such as amiodarone and Tylenol.

Additionally, bicalutamide is an inhibitor of the CYP3A4 hepatic enzymes (Evered et al., 2020; Cocksshott, 2004). The bicalutamide-induced inhibition of CYP3A4 can increase plasma concentrations of midazolam given during the perioperative period, extending its pharmacological effects and leading to increased sedation (Evered et al., 2020; Bailey et al.,

2020). Bicalutamide may also displace warfarin from its protein binding site. This will increase the active portion of warfarin and increase the risk of surgical bleeding during the perioperative period (Evered et al., 2020; Araki et al., 2019). The anesthesia provider must be aware of this potential complication and relay this knowledge to the surgical team.

The administration of anti-androgens has also been noted to result in increased cardiac risks during the perioperative period. Testosterone blocking drugs, such as bicalutamide and cyproterone prolong the heart's QT interval placing the patient at risk for the development of severe heart rhythm abnormalities, such as torsades de pointes and sudden death (Aalem et al., 2019; Angus et al.,2023; Gagliano-Jucá et al., 2019). Life threatening arrhythmias from antiandrogen administration is rare in the transgender patient; however, the anesthesia provider must be aware of this potential risk when forming the anesthetic plan. It is imperative that the anesthesia provider assesses the QT interval length on the ECG and monitors it throughout the perioperative period. The anesthesia should use caution when administering other medications known to prolong the QT interval. Drugs known to prolong the QT interval that are commonly administered in the perioperative period include antiemetics (droperidol and ondansetron), Antipsychotics (haloperidol), and antibiotics (fluoroquinolones and macrolides) (Farzam & Tivakaran, 2023). A thorough preoperative assessment and medication reconciliation is vital for provider awareness of potential perioperative complications as a result of medication interactions.

Other medications commonly administered during the perioperative period can also interact with HRT. The administration of the neuromuscular blocking reversal agent Bridion (Sugammadex) decreases the efficacy of estrogen-containing birth control and has the potential to interact with HRT. The CRNA should avoid its administration in transgender individuals to

decrease the potential for withdrawal symptoms (Harper & Maiorino, 2022).

Risk of Altered Respiratory Physiology

Chest binding involves using tight material to compress chest tissue to obtain a flat chest appearance. It is a common practice among transgender men and is used as early as 18 years old (Cumming et al., 2016; Peitzmeier et al., 2021). Though it promotes identity and gender euphoria, there are also important implications to respiratory physiology. Chest pain, shortness of breath, and rib fractures are common complaints. Additionally, its use may promote a restrictive lung disease pattern of breathing over time as lung volumes and capacities are overall reduced with a high FEV1/FVC ratio (Cumming et al., 2016; Shah et al., 2019; Tollinche et al., 2020). Though the long-term effects of chest binding are unknown, ventilatory management must be tailored to restrictive respiratory patterns. (Ferrando et al., 2022; Tollinche et al., 2020).

Preoperative assessment of chest binding practices in transgender men is an important consideration which will guide the anesthetic approach. Induction is best performed in head-up position (reverse Trendelenburg) given the patient's reduced functional residual capacity (FRC) involved with restrictive lung patterns. Prolonged periods of apnea during induction should also be avoided due to the reduced FRC.

Intraoperative ventilatory goals include reducing intrathoracic pressure to avoid barotrauma, volutrauma, and reduced venous return. Adequate anesthetic depth and neuromuscular paralysis is key for ventilatory compliance and avoidance of high peak pressures. Additionally, use of low tidal volumes (6 mL/kg) avoids high intrathoracic pressures. To offset potential respiratory acidosis associated with low tidal volumes, an increase in respiratory rate should be employed to maintain carbon dioxide levels within normal limits.

Plan for emergence and tracheal extubation should resemble that of a patient with chronic

restrictive lung disease. The patient should be in a head-up position as appropriate, ensure adequate neuromuscular blockade reversal, and establish an alert and cooperative patient. Caution should be taken with long-term opioids and benzodiazepines as they may contribute to poor respiratory effort postoperatively (Gruenbaum & Kurup, 2021).

Difficult Airway

Many transgender individuals undergo GAS such as laryngoplasty and/or chondroplasty for aesthetic or voice modifying purposes (Leinung & Joseph, 2020; Nolan et al., 2021). The anatomical changes as a result of these procedures pose challenges in the perioperative setting as cases of airway complications have reportedly occurred. (Lao & Crawley, 2020; Vowles et al., 2020). Airway complications include airway trauma, tracheal stenosis, surgical narrowing of the glottis, and vocal cord damage. The procedures also result in scarring or loss of the cricothyroid membranous space making emergency airway access challenging (Lao & Crawley, 2020; Tollinche et al., 2020; Vowles et al., 2020). It is prudent that the anesthesia provider is aware of past surgical history involving the patient's airway in order to anticipate and plan for difficult airway scenarios. The anesthetic plan should consider careful atraumatic intubation, the use of video laryngoscopy, and the availability of the difficult airway cart.

When compared to the biological male, the airway anatomy of a biological female is generally smaller, necessitating a smaller diameter endotracheal tube (ETT) such as size 6.0-7.0 millimeter internal diameter (Barnett et al., 2020). To avoid airway trauma, the anesthesia provider needs to consider the patient's biological sex for ETT selection. If the provider does not consider the patient's biological sex, selection of an ETT that is too large for the patient's anatomy may result in both unexpected difficult airway situations and post-operative airway trauma (Lao & Crawley, 2020; Vowles et al., 2020). In FTM transgender patients, a smaller

sized ETT is preferred to prevent post-intubation complications (Friedlander et al., 1999; Lao & Crawley, 2020). Avoidance of airway complications necessitates awareness, vigilance, and patient-specific knowledge. Thus, the transgender individual's airway assessment must directly address the patient's GAS surgical history and use of HRT (Lao & Crawley, 2020; Vowles et al., 2020).

Theoretical Framework

The gap analysis model by Leonard and Bottorf was used and provided the template for the planning of this scholarly project. Leonard and Bottorf (2022) outline the steps as: identify the current state, set S.M.A.R.T. goals to reach desired state, analyze the gap, and establish a plan to close the existing gap.

Project Aims

The primary aim of this scholarly project was to provide knowledge for nurse anesthetists of perioperative complications for transgender patients on HRT or gender confirming practices by developing an evidence-based online module approved for CE credit submitted for approval to the American Association of Nurse Anesthesiology (AANA). The project's objectives are as follows:

1. Complete an evidence-based one-hour online module, including pretest and posttest, by the investigators in collaboration with Echelon platform on the care of the transgender patient on HRT or gender confirming procedures and practices by April 2023.
2. Provide education on the perioperative complications in the transgender population undergoing HRT or gender confirming procedures and practices and include evidence-based recommendations regarding their care by March 2024.
3. Apply for CE credit approval by the AANA by December 2023.

Methods

This scholarly project was conducted in the Echelon division of AHU. Gap analysis was used to compare the current state to the desired state in healthcare (Fourie et al., 2021; Thompson et al., 2008). The framework developed by Leonard and Bottorf analyzed the current state, identified the desired state, and found the gap, and helped investigators create a plan to bridge that gap.

Identify the Current State

A gap exists between safe transgender patient care and didactic transgender education (Dy et al., 2016; Johnston & Shearer, 2017; Unger, 2015). It is estimated that 0.6% of the United States population identifies as transgender, yet this population suffers from numerous health disparities as a result of a lack in provider training, education, and comfort in caring for these individuals (Dy et al., 2016; Johnston & Shearer, 2017; Roque et al., 2021). Within postgraduate medical training there is an absence of standardized curriculum dedicated to the transgender patient population, with the majority of institutions providing no education on the subject (Dividge-Pitts et al., 2017; Dy et al., 2016; Roque et al., 2021; Unger, 2015). Specifically, formal anesthesia training does not require a curriculum addressing transgender patients and their perioperative care (Peterson, 2020; Roque et al., 2021). The lack of education contributes to the provider's discomfort with implementing appropriate population-specific patient care (Johnston & Shearer, 2017; Unger, 2015). The lack of provider preparation necessitates education on transgender patients during the perioperative period (Davidge-Pitts et al., 2017; Roque et al., 2021).

Set S.M.A.R.T. Goals to Reach Desired State

The objectives are S.M.A.R.T. goals that helped focus the direction of this scholarly

project. The CE module was the medium for the information. Application for CE credit with the AANA will help the module reach a wide audience. The evidenced-based recommendations will be included with local dissemination.

Analyze the gap

The gap in transgender care stems from the lack of formal education given that this is an emerging topic in healthcare. An increase in knowledge is provided by developing an evidence-based CE module on the associated perioperative complications of transgender patients. The CE module addressed the knowledge gap in respect to this unique population, leading to a greater provider awareness.

Establish a Plan to Close the Gap

The creation of a CE module will help close the gap between the current state and desired state. Instructions and guidance were given to the investigators through video conference calls which were recorded and stored in password protected laptops to determine the procedure, time, resources, barriers, and facilitators needed as part of the coursework. The investigators obtained verbal consent from all participants prior to recording the interviews. All communication obtained will be destroyed after seven years. There were no human subjects in this project; therefore, there were no ethical considerations such as consent, notice of voluntary participation, or compensation for participation. The CE module was developed and distributed through Echelon. When completed, an accreditation packet was created and submitted to the AANA for accreditation.

Planning & Procedures

Planning

Planning began with a literature review of the topic. Interviews were conducted with

several key players. Lori Polizzi, Director of Echelon at AHU, is the main contact with Echelon who guided the development of the CE module. Bibidh Subedi, PharmD, RPh works at AdventHealth Orlando in the intensive care units. His insight in drug therapy and regimen was a valuable resource throughout the scholarly project.

Implementation

The development of the CE module began after gaining approval from the site director. The topics addressed came from the literature review and synthesis of evidence. After a transcript was written and approved, the design team created the images and graphics that accompanied the CE module. It was submitted to the AANA and gained CE credit approval.

Barriers and Facilitators

Time was the main barrier for this scholarly project. The development of the CE module required multiple drafts which required feedback from Echelon. As a facilitator, Lori Polizzi provided expert guidance on the creation of a CE module and helped to submit it for AANA credit. Dr. Jill Mason, project chain, along with the project committee members also played a key role in facilitating the project by adding valuable input and reviewing the content of the CE module.

Procedures to Sustain

The CE module, after AANA approval, has CE credit for two years. This allows the information to reach the target audience. Since this is an emerging topic, it may be the first time that anesthesia providers have been made aware of the topic, bringing to light its educational necessity, which may allow for more research in this area.

Timeline

The project topic was first approved in March 2022 by AdventHealth University's (AHU)

Department of Nurse Anesthesia Practice faculty, and the site was identified as Echelon. A scholarly project committee was formed in August 2022 to aid in the success of this process. This proposal paper was completed and submitted by December 2022 to the Scientific Review Committee and the Institutional Review Board with exception as there are no human subjects. Implementation began in January 2023 with the development of the CE module and was completed by June 2023. Then, the CE module was submitted for AANA credit by June 2023. Dissemination will then be completed in March 2024.

Budget/Grant

There is no budget for this scholarly project.

Discussion and Implications

Applicability to Practice

As the transgender population gains acceptance and visibility, it is likely that more transgender patients will be seen in the operating room. Educating anesthesia providers on the effects of HRT and GAS such as risk for VTE, cardiovascular complications, medication interactions, and altered airway will allow for a more thorough medical and surgical history leading to a better tailored anesthetic plan (Vowles et al., 2020). Understanding the effects of HRT allows for the anesthesia provider to be more vigilant and better prepared for intraoperative complications such as PE, MI, and CVA. For those patients who practice chest binding, the anesthesia provider will be able to better plan for induction, intraoperative ventilatory goals, and emergence. As airway experts, the anesthesia providers' awareness of the potential airway complications when caring for transgender patients who have undergone GAS will help avoid the negative outcomes associated with difficult intubations and airway trauma (Lao & Crawley, 2020; Vowles et al., 2020).

An increased knowledge of the potential complications of HRT and GAS allows the anesthesia provider to provide safe and competent care. Specific to CRNAs, this aligns with the American Association of Nurse Anesthesiology (AANA) Standards for Nurse Anesthesia Practice II, III, VII, and XIV. Standards II, III, VII delineate a thorough preoperative evaluation and an appropriate plan that is fundamental to the delivery and implementation of safe care. It includes an understanding of the potential complications that may occur in the transgender population as a result of gender-affirming procedures/practices and HRT. Finally, standard XIV discusses the culture of safety starting with the CRNA being appropriately educated which will promote awareness among the perioperative team members related to the care of the transgender individual (AANA, 2019).

Limitations

Perioperative complications in the transgender population is an emerging topic in healthcare; therefore, the literature is limited. Much of the information and evidence encountered in the literature related to the transgender population included case studies and studies with small sample sizes which decreased its generalizability related to the conclusions found in them. No randomized controlled trials have been conducted thus far, and the current studies included were retrospective. Some of the data also came from the cisgender population.

Conclusion

As access and coverage increases, the likelihood that anesthesia providers will encounter transgender individuals in the perioperative setting increases. From what can be concluded from the literature, transgender surgical patients are at an increased risk for cardiovascular complications from HRT, experience potential drug interactions related to HRT, may have altered respiratory physiology, and potentially difficult airway related to airway GAS. Currently

there is a gap in evidence-based guidelines to care for this patient population as well as a lack of standardized curriculum in postgraduate medical training. The creation of a CE module related to the transgender patient and perioperative complications addresses this gap. This CE module provides insight to the potential complications and evidence-based recommendations in the care and management of the transgender surgical patient who has undergone critical treatment modalities.

Dissemination Plan

This scholarly project will be disseminated at a national level by submitting for approval for CE credit by the AANA by December 2023. It will also be shared locally at AHU as a poster presentation and a PowerPoint presentation shared through the Canvas learning platform in March 2024.

References

AANA. (2019). *Standards for Nurse Anesthesia Practice*. Retrieved October 2, 2022, from https://www.aana.com/docs/default-source/practice-aana-com-web-documents-(all)/professional-practice-manual/standards-for-nurse-anesthesia-practice.pdf?sfvrsn=e00049b1_18

Al-Hameed, F., Al-Dorzi, M., Qadhi, A. I., Shaker, A., Al-Gahtani, H., Al-Jassir, F., Zahir, F., Al-Khuwaitir, S., Addar, H., Al-Hajjaj, S., Abdelaal, A., & Aboelnazar, Y. (2017). Thromboprophylaxis and mortality among patients who developed venous thromboembolism in seven major hospitals in Saudi Arabia. *Annals of Thoracic Medicine, 12*(4), 282–289. https://doi.org/10.4103/atm.ATM_101_17

Alzahrani, T., Nguyen, T., Ryan, A., Dwairy, A., McCaffrey, J., Yunus, R., Forgione, J., Krepp, J., Nagy, C., Mazhari, R., & Reiner, J. (2019). Cardiovascular disease risk factors and myocardial infarction in the transgender population. *Circulation: Cardiovascular Quality and Outcomes*, *12*(4), 1-7. https://www.doi.org/10.1161/CIRCOUTCOMES.119.005597

Anderson, F. & Spencer, F. (2003). Risk factors for thromboembolism. *American Heart Association, 107*(23), 9-16. https://doi.org/10.1161/01.CIR.0000078469.07362.E6

Angus, L., Grossmann, M., Lin, T., Leemaq, L., & Zajac, J., (2023). Feminising gender affirming hormone therapy prolongs QTc interval. *Journal of the Endocrine Society, 7*(1), https://doi.org/10.1210/jendso/bvad114.2084

Araki, Y., Kawaguchi, O., Konishi, Y., & Terada, T. (2019). Extreme elevation of the prothrombin time-international normalized ratio due to a probable interaction between warfarin and flutamide. *Internal medicine (Tokyo, Japan), 58*(22), 3251–3253. https://doi.org/10.2169/internalmedicine.2973-19

Bailey, D., Dresser, G., & Spence, J. (2000). Pharmacokinetic-Pharmacodynamic Consequences and Clinical Relevance of Cytochrome P450 3A4 Inhibition. *Clin Pharmacokinet, 38*, 41–57. https://doi.org/10.2165/00003088-200038010-00003

Barnett, W., Mudiyanselage, P., Haghbin, H., Banifadel, M., Adunse, J., Safi, F., & Assaly, R. (2020). Larger endotracheal tube size in women increase the risk for ventilator-associated events. *Infect Control Hospital Epidemiology*, *41*(5), 618-619. https://doi.org/10.1017/ice.2020.50

Bergendal, A., Kieler, H., Sundström, A., Hirschberg, L., & Kocoska-Maras, L. (2016). Risk of venous thromboembolism associated with local and systemic use of hormone therapy in peri- and postmenopausal women and in relation to type and route of administration. *Menopause*, *23*(6), 593-599. https://doi.org/10.1097/GME.0000000000000611

Bjornsdottir, E., Bjornsson, E. & Gretarsdottir, H. (2018). Bicalutamide-Associated Acute Liver Injury and Migratory Arthralgia: A Rare but Clinically Important Adverse Effect. *Case Reports in Gastroenterology*, *12*(2), 266. http://dx.doi.org.resource.ahu.edu/10.1159/000485175

Boskey, E. R., Taghinia, A. H., & Ganor, O. (2019). Association of surgical risk with exogenous hormone use in transgender patients: A systematic review. *JAMA Surgery, 154*(2), 159–169. https://doi.org/10.1001/jamasurg.2018.4598

Canner, J. K., Harfouch, O., Kodadek, L. M., Pelaez, D., Coon, D., Offodile, A. C., Haider, A. H., & Lau, B. D. (2018). Temporal trends in gender-affirming surgery among transgender patients in the United States. *JAMA Surgery*, *153*(7), 609–616. https://doi.org/10.1001/jamasurg.2017.6231

Casimiro, I. & Cohen, R., (2019). Severe vasomotor symptoms post-oophorectomy despite

testosterone therapy in a transgender man: A unique case study. *Journal of the Endocrine Society*, *4*(3), 734–736. https://doi.org/10.1210/js.2018-00367

Chalhoub, V., Edelman, P., Staiti, G., & Benhamou, D. (2008). Contraception orale, traitement hormonal de la menopause: Risque thromboembolique et implications périopératoires [Oral contraception and hormone replacement therapy: Management of their thromboembolic risk in the perioperative period]. *Annales Francaises d'Anesthesie et de Reanimation*, *27*(5), 405–415. https://doi.org/10.1016/j.annfar.2008.04.002

Chan, W., Drummond, A., & Kelly, M. (2017). Deep vein thrombosis in a transgender woman. *CMAJ : Canadian Medical Association- journal de l'Association medicale canadienne*, *189*(13), E502–E504. https://doi.org/10.1503/cmaj.160408

Clark, R. E. & Estes, F. (2008). *Turning research into results: A guide to selecting the right performance solutions*. CEP Press.

Cockshott I. D. (2004). Bicalutamide: clinical pharmacokinetics and metabolism. *Clinical pharmacokinetics*, *43*(13), 855–878. https://doi.org/10.2165/00003088-200443130-00003

Cohn, S. L. & Fleisher, L. A. (2021). Evaluation of cardiac risk prior to noncardiac surgery. *UpToDate*. Retrieved September 5, 2022, from https://www.uptodate.com/contents/evaluation-of-cardiac-risk-prior-to-noncardiac-surgery

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., Fraser, L., Green, J., Knudson, G., Meyer, W. J., Monstrey, S., Adler, R. K., Brown, G. R., Devor, A. H., Ehrbar, R., Ettner, R., Eyler, E., Garofalo, R., Karasic, D. H., . . . Zucker, K. (2012). Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *International Journal of Transgenderism*, *13*(4), 165-

232. https://doi.org/10.1080/15532739.2011.700873

Cook, T. M., & MacDougall-Davis, S. R. (2012). Complications and failure of airway management. *British Journal of Anaesthesia*, (*109 Suppl 1)*, i68–i85. https://doi.org/10.1093/bja/aes393

Cumming, R. J. M., Sylvester, K., & Fuld, J. (2016). Understanding the effects on lung function of chest binder use in the transgender population. *British Medical Journal Thorax, 71*(3), A227. https://doi.org/10.1136/thoraxjnl-2016-209333.400

Dalton, M., Lees, T., & Sachdeva, A. (2018). Graduated compression stockings for prevention of deep vein thrombosis. *The Cochrane database of systematic reviews*, *11*(11), CD001484. https://doi.org/10.1002/14651858.CD001484.pub4

Davidge-Pitts, C., Nippoldt, T. B., Danoff, A., Radziejewski, L., & Natt, N. (2017). Transgender health in endocrinology: Current status of endocrinology fellowship programs and practicing clinicians. *The Journal of Clinical Endocrinology & Metabolism*, *102*(4), 1286-1290. https://doi.org/10.1210/jc.2016-3007

den Heijer, M. & Tangpricha, V. (2017). Oestrogen and anti-androgen therapy for transgender women. The lancet. *Diabetes & endocrinology, 5*(4), 291–300. https://doi.org/10.1016/S2213-8587(16)30319-9

Desciak, M. C., Martin, D. E. (2011). Perioperative pulmonary embolism: diagnosis and anesthetic management. *Journal of Clinical Anesthesia*, 23, 153-165. https://doi.org/10.1016/j.jclinane.2010.06.011

Devereaux, P.J., Goldman, L., Cook, D.J., Gilbert, K., Leslie, K., & Guyatt, G.H. (2005). *Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and*

communicate risk. CMAJ. 173 (6), 627-634. http://www.doi.org/10.1503/cmaj.050011

Dutra, E., Lee, J., Torbati, T., Garcia, M., Merz, C. N. B., & Shufelt, C. (2019). Cardiovascular implications of gender-affirming hormone treatment in the transgender population. *Maturitas*, *129*, 45-49. https://www.doi.org/10.1016/j.maturitas.2019.08.010

Dy, G. W., Osbun, N. C., Morrison, S. D., Grant, D. W., Merguerian, P. A., & Transgender Education Study Group. (2016). Exposure to and attitudes regarding transgender education among urology residents. *The Journal of Sexual Medicine*, *13*(10), 1466-1472. https://doi.org/10.1016/j.jsxm.2016.07.017

Evered, L. Lennie, Y.,& Leareng, K. (2020). Perioperative considerations for transgender women undergoing routine surgery: a narrative review. *British journal of anaesthesia*, *124*(6), 702–711. https://doi.org/10.1016/j.bja.2020.01.024

Farzam K. & Tivakaran V.(2023). QT Prolonging Drugs. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK534864/

Ferrando, C., Zhao, L. C., & Nikolavsky, D. (2022). Gender-affirming surgery: Female to male. *UpToDate.* Retrieved June 5, 2022, from https://www.uptodate.com/contents/gender-affirming-surgery-female-to-male

Flores, A. R., Herman, J. L., Gates, G. J., & Brown, T. N. T. (2016). *How many adults identify as transgender in the United States?* Williams Institute. https://williamsinstitute.law.ucla.edu/publications/trans-adults-united-states/

Fourie, A., Ahtiala, M., Black, J., Hevia, H., Coyer, F., Gefen, A., LeBlanc, K., Smet, S., Vollman, K., Walsh, Y., & Beeckman, D. (2021). Skin damage prevention in the prone ventilated critically ill patient: A comprehensive review and gap analysis (PRONETECT study). *Journal of Tissue Viability*, *30*(4), 466–477.

https://doi.org/10.1016/j.jtv.2021.09.005

Friedlander, P., Aygene, E., & Kraus, D. H. (1999). Prevention of airway complications in thyroplasty patients requiring endotracheal intubation. *The Annals of Otology, Rhinology, and Laryngology, 108*(8), 735–737. https://doi.org/10.1177/000348949910800804

Gaither, T. W., Awad, M. A., Osterberg, E. C., Murphy, G. P., Romero, A., Bowers, M. L., & Breyer, B. N. (2018). Postoperative complications following primary penile inversion vaginoplasty among 330 male-to-female transgender patients. *The Journal of Urology, 199*(3), 760–765. https://doi.org/10.1016/j.juro.2017.10.013

Gagliano-Jucá, T., Travison, T. G., Kantoff, P. W., Nguyen, P. L., Taplin, M. E., Kibel, A. S., Huang, G., Bearup, R., Schram, H., Manley, R., Beleva, Y. M., Edwards, R. R., & Basaria, S. (2018). Androgen Deprivation Therapy Is Associated With Prolongation of QTc Interval in Men With Prostate Cancer. *Journal of the Endocrine Society*, *2*(5), 485–496. https://doi.org/10.1210/js.2018-00039

Gruenbaum, S. & Kurup, V. (2021). Anesthesia for patients with interstitial lung disease or other restrictive disorders. *UpToDate.* Retrieved September 5, 2022, from https://www.uptodate.com/contents/anesthesia-for-patients-with-interstitial-lung-disease-or-other-restrictive-disorders#H1639444393

Hatfield, M. G. (2017). *Anesthesia providers' discovery of patients' gender identity*. The University of Arizona.

Harper, K. D., & Maiorino, E. (2022). Total joint arthroplasties in transgender patients: Unique considerations for an emerging patient population. *Journal of the American Academy of Orthopaedic Surgeons, 30*(13), 607-612. https://doi.org/10.5435/JAAOS-D-21-00914

Haveles, C. S., Wang, M. M., Arjun, A., Zaila, K. E., & Lee, J. C. (2021). Effect of cross-sex

hormone therapy on venous thromboembolism risk in male-to-female gender-affirming surgery. *Annals of Plastic Surgery*, *86*(1), 109–114. https://doi.org/10.1097/sap.0000000000002300

Hayes, H., Haugen, A., Nagavally, S., & Russell, R., Sarvaideo, J. (2022). The Utility of Monitoring Potassium in Transgender, Gender Diverse, and Nonbinary Individuals on Spironolactone. *Journal of the Endocrine Society*, *6*(11), bvac133. https://doi.org/10.1210/jendso/bvac133

Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *102*(11), 3869–3903. https://doi.org/10.1210/jc.2017-01658

Hensley, N. B. & Hogue, C. W. (2022). Anesthesia for noncardiac surgery in patients with ischemic heart disease. *UpToDate.* Retrieved September 5, 2022, from https://www.uptodate.com/contents/anesthesia-for-noncardiac-surgery-in-patients-with-ischemic-heart-disease

ISTH Steering Committee for World Thrombosis Day (2016). Venous thromboembolism: A Call for risk assessment in all hospitalised patients. *Thrombosis and haemostasis*, *116*(5), 777–779. https://doi.org/10.1160/TH16-09-0732

James, S. E., Herman, J. L., Rankin, S., Keisling, M., Mottet, L., & Anafi, M. (2016). *The Report of the 2015 U.S. Transgender Survey*. National Center for Transgender Equality. https://www.ustranssurvey.org/reports

Johnston, C. D., & Shearer, L. S. (2017). Internal medicine resident attitudes, prior education,

comfort, and knowledge regarding delivering comprehensive primary care to transgender patients. *Transgender health*, *2*(1), 91–95. https://doi.org/10.1089/trgh.2017.0007

Kain, R., Kaushal, A. Mihra, P., & Nath A. (2021). Gender reassignment surgery: A narrative overview of anesthetic considerations and implications. *Anaesthesiology Intensive Therapy, 54*(4), 343-349. https://doi.org/10.5114/ait.2021.109446

Kotamarti, V. S., Greige, N., Heiman, A. J., Patel, A., & Ricci, J. A. (2021). Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: A systematic review. *The Journal of Sexual Medicine, 18*(7), 1280-1291. https://doi.org/10.1016/j.jsxm.2021.04.006

Kozato, A., Fox, G. W. C., Yong, P. C., Shin, S. J., Avanessian, B. K., Ting, J., Ling, Y., Karim, S., Safer, J. D., & Pang, J. H. (2021). No venous thromboembolism increase among transgender female patients remaining on estrogen for gender-affirming surgery. *The Journal of Clinical Endocrinology and Metabolism, 106*(4), e1586–e1590. https://doi.org/https://doi.org/10.1210/clinem/dgaa966

Kumar, P., Reddy, S., Kulkarni, A., Sharma, M., & Rao, P. N. (2021). Cyproterone Acetate-Induced Acute Liver Failure: A Case Report and Review of the Literature. *Journal of clinical and experimental hepatology*, *11*(6), 739–741. https://doi.org/10.1016/j.jceh.2021.01.003

Lao, W. P., & Crawley, B. K. (2020). Airway considerations in transgender patients: Complicated intubation. *Ear, Nose, & Throat Journal*, *100*(5_suppl), 755S-756S. https://doi.org/10.1177/0145561320910680

Lawrence, A. A. (2006). Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Archives of Sexual Behavior, 35*(6), 717–727.

https://doi.org/10.1007/s10508-006-9104-9

Leinung, M. C., & Joseph, J. (2020). Changing demographics in transgender individuals seeking hormonal therapy: Are trans women more common than trans men? *Transgender health*, *5*(4), 241–245. https://doi.org/10.1089/trgh.2019.0070

Lee, C. H., Cheng, C. L., Kao Yang, Y. H., & Lin, L. J. (2015). Hormone therapy and risk of venous thromboembolism among postmenopausal women in Taiwan - A 10-year nationwide population-based study. *Circulation Journal: Official Journal of the Japanese Circulation Society*, *79*(5), 1107–1114. https://doi.org/10.1253/circj.CJ-14-1227

Mani, V. R., Valdivieso, S. C., Hanandeh, A., Kalabin, A., Ramcharan, A., & Donaldson, B. (2021). Transgender surgery - Knowledge gap among physicians impacting patient care. *Current Urology*, *15*(1), 68–70. https://doi.org/10.1097/CU9.0000000000000002

Miskovic, A., & Lumb, A. B. (2017). Postoperative pulmonary complications. *British Journal of Anaesthesia*, *118*(3), 317–334. https://doi.org/10.1093/bja/aex002

Nemeth, B., Lijfering, W. M., Nelissen, R., Schipper, I. B., Rosendaal, F. R., le Cessie, S., & Cannegieter, S. C. (2019). Risk and risk factors associated with recurrent venous thromboembolism following surgery in patients with history of venous thromboembolism. *JAMA network open*, *2*(5), e193690. https://doi.org/10.1001/jamanetworkopen.2019.3690

Nolan, B. J., & Cheung, A. S. (2020). Estradiol therapy in the perioperative period: Implications for transgender people undergoing feminizing hormone therapy. *The Yale Journal of Biology & Medicine*, *93*(4), 539-548.

Nolan, I. T., Haley, C., Morrison, S. D., Pannucci, C. J., & Satterwhite, T. (2021). Estrogen continuation and venous thromboembolism in penile inversion vaginoplasty. *Journal of*

Sexual Medicine, 18(1), 193-200. https://doi.org/10.1016/j.jsxm.2020.10.018

Peitzmeier, S.M., Silberholz, J., Gardner, I.H., Weinand, J., & Acevedo, K. (2021). Time to first onset of chest binding–related symptoms in transgender youth. *Pediatrics*, *147*(3), 1-7. https://doi.org/10.1542/peds.2020-0728

Peterson, M. I. (2020). *Increasing Certified Registered Nurse Anesthetist (CRNA) Knowledge and Comfort in the Care of Transgender Patients* (Doctoral dissertation, University of Michigan-Flint).

Prior, J.C., Vigna, Y.M. & Watson, D. (1989). Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Arch Sex Behav , 18*, 49–57.https://doi.org/10.1007/BF01579291

Roque, R. A., O'Reilly-Shah, V., Lorello, G. R., Adams, T., & Cladis, F. (2021). Transgender patient care: A prospective survey of pediatric anesthesiologist attitudes and knowledge. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*, *68*(11), 1723-1726.

Salem, J. E., Yang, T., Moslehi, J. J., Waintraub, X., Gandjbakhch, E., Bachelot, A., Hidden-Lucet, F., Hulot, J. S., Knollmann, B. C., Lebrun-Vignes, B., Funck-Brentano, C., Glazer, A. M., & Roden, D. M. (2019). Androgenic Effects on Ventricular Repolarization: A Translational Study From the International Pharmacovigilance Database to iPSC-Cardiomyocytes. *Circulation*, *140*(13), 1070–1080. https://doi.org/10.1161/CIRCULATIONAHA.119.040162

Sazgary, L., Puelacher, C., Lurati-Buse, G., Glarner, N., Lampart A, Bolliger D, Steiner L, Gürke L, Wolff T, Mujagic E, Schaeren S, Lardinois D, Espinola J, Kindler C, Hammerer-Lercher A, Strebel I, Wildi K, Hidvegi R, Gueckel J, Hollenstein C, Breidthardt T, Rentsch K, Buser A, Gualandro DM, Mueller C. (2020). Incidence of

major adverse cardiac events following non-cardiac surgery. *European Heart Journal Acute Cardiovasc Care*. 10 (5), 550–558. https://doi.org/10.1093/ehjacc/zuaa008

Shah, B. S., Khanna, P., Bhatt, R., Goyal, P., Garg, R., & Chawla, R. (2019). Perioperative anaesthetic concerns in transgender patients: Indian perspective. *Indian Journal of Anaesthesia, 63*(2), 84-91. https://doi.org/10.4103/ija.IJA_640_18

Shiffman M. A. (2003). Estrogen and thromboembolic disorders: Should patients stop hormones prior to cosmetic surgery? *Journal of Women's Health, 12*(9), 853–855. https://doi.org/10.1089/154099903770948078

Streed, J., Carl, G., Harfouch, O., Marvel, F., Blumenthal, R. S., Martin, S. S., & Mukherjee, M. (2017). Cardiovascular disease among transgender adults receiving hormone therapy: A narrative review. *Annals of Internal Medicine, 167*(4), 256-267. https://doi.org/10.7326/M17-0577

Thompson, A., Brennan, K., Cox, A., Gee, J., Harcourt, D., Harris, A., Harvie, M., Holen, I., Howell, A., Nicholson, R., Steel, M., & Streuli, C. (2008). Evaluation of the current knowledge limitations in breast cancer research: A gap analysis. *Breast Cancer Research, 10*(2). https://doi.org/10.1186/bcr1983

Tollinche, L. E., Van Rooyen, C., Afonso, A., Fischer, G. W., & Yeoh, C. B. (2020). Considerations for transgender patients perioperatively. *Anesthesiology Clinics, 38*(2), 311-326. https://doi.org/10.1016/j.anclin.2020.01.009

Unger, C. A. (2016). Hormone therapy for transgender patients. *Translational andrology and urology, 5*(6), 877–884. https://doi.org/10.21037/tau.2016.09.04

Unger, C. A. (2015). Care of the transgender patient: a survey of gynecologists' current knowledge and practice. *Journal of women's health, 24*(2), 114-118.

Vowles, B. J., Ahmad, I., & Christodoulides, G. (2020). Unexpected difficult airway management in a transgender female patient. *Anaesthesia Reports*, *8*(1), 36-39. https://doi.org/10.1002/anr3.12042

Wierckx, K., Elaut, E., Declercq, E., Heylens, G., De Cuypere, G., Taes, Y., Kaufman, J. M., & T'Sjoen, G. (2013). Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: A case-control study. *European Journal of Endocrinology*, *169*(4), 471-478. https://www.doi.org/10.1530/EJE-13-0493

Appendix A: Matrix Tables

<table>
<tr><td colspan="6">References
Lao, W. P., & Crawley, B. K. (2020). Airway considerations in transgender patients: Complicated intubation. Ear, Nose, & Throat Journal, 100(5_suppl), 755S-756S. https://doi.org/10.1177/0145561320910680
Vowles, B. J., Ahmad, I., & Christodoulides, G. (2020). Unexpected difficult airway management in a transgender female patient. Anaesthesia Reports, 8(1), 36-39. https://doi.org/10.1002/anr3.12042</td></tr>
<tr><td>Purpose</td><td>Variables</td><td>Setting/Subjects</td><td>Measurement and Instruments</td><td>Results</td><td>Evidence Quality</td></tr>
<tr><td>Study One:
To present a case of serious complications due to inappropriate endotracheal tube selection in a transgender patient

Study Two:
To present a case of an unexpected difficult airway due to scar tissue that developed after a facial feminization surgery.

Design
Study One:
case study

Study Two:
case study</td><td>Study One:
Primary Outcome:
tracheal damage due to inappropriate size endotracheal tube

Secondary Outcome:
n/a

Study Two:
Primary Outcome:
unexpected difficult airway management

Secondary Outcome:
n/a</td><td>Study One:
Setting: Loma Linda University Medical Center

Subject: 25-year-old biologically female, male transgender patient

Study Two:
Setting: the setting was not described

Subject: 51-year-old transgender female scheduled to undergo sternotomy for thymectomy and left upper lobe wedge resection.</td><td>Study One:
The patient was diagnosed with tracheal stenosis via an airway exam under anesthesia that was 2 cm in length beginning 3.2 cm below the vocal fold.

Study Two:
Direct laryngoscopy with a C-MAC. A D-blade was used to gain a view of the arytenoid cartilages and posterior aspect of the glottic opening.</td><td>Study One:
Patient required excision of scarring, balloon dilation, steroid, mitomycin C to increase the luminal diameter. Additional dilations were required after.
Study Two:
Patient required dexamethasone and adrenaline to reduce swelling before successful extubation.

Implications
Study One:
Providers need to take into considerations patients’ biological sex when choosing endotracheal tube size to avoid postintubation complications.
Study Two:
Increased need of education for anesthesia providers on possible difficult airway after gender confirming surgery.</td><td>Study One:
Methodological flaws: single case study. Patient was lost to follow up after the fourth dilation.
Inconsistency: none
Indirectness: none
Imprecision: small sample size
Publication bias: none

Study Two:
Methodological flaws: case study
Inconsistency: patient did not disclose history of airway procedures
Indirectness: none
Imprecision: small sample size
Publication bias: none</td></tr>
</table>

<table>
<tr><td colspan="6">References
Gaither, T. W., Awad, M. A., Osterberg, E. C., Murphy, G. P., Romero, A., Bowers, M. L., & Breyer, B. N. (2018). Postoperative complications following primary penile inversion vaginoplasty among 330 male-to-female transgender patients. The Journal of Urology, 199(3), 760.
Lawrence, A. A. (2006). Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Archives of Sexual Behavior, 35(6), 717.</td></tr>
<tr><td>Purpose</td><td>Variables</td><td>Setting/Subjects</td><td>Measurement and Instruments</td><td>Results</td><td>Evidence Quality</td></tr>
<tr><td>Study One:
To determine whether age, BMI, and years on hormone replacement therapy are risk factors for perioperative complications after penile inversion vaginoplasty.

Study Two:
To determine perioperative complications and outcomes of male to female sex reassignment surgery.

Design
Study One:
Retrospective chart review

Study Two:
Survey</td><td>Study One:
<u>Primary outcome</u>:
age, BMI, and years on hormone replacement therapy in relation to DVT, PE, wound healing, infection

<u>Secondary outcome</u>:
n/a

Study Two:
<u>Primary outcome</u>:
evaluate patients' reported use of hormone therapy and DVT rate after surgery

<u>Secondary outcome</u>:
n/a</td><td>Study One:
<u>Setting</u>: Department of Urology, University of California-San Francisco, San Francisco General Hospital

<u>Subjects</u>: 330 patients from 2011 to 2015

Study Two:
<u>Setting</u>: patients of Dr. Toby Meltzer in Portland, Oregon

<u>Subjects</u>: 232 patients that undergone penile inversion vaginoplasty and sensate clitoroplasty</td><td>Study One:
Data analysis was performed with STATA, version 13.0. Statistical significance was considered at $p < 0.05$.

Study Two:
Mailed questionnaire and returned anonymously. Measurements were patient satisfaction, whether they stopped taking hormone or not, any complications, what year they had surgery, any additional surgeries, whether they had undergone electrolysis of scrotum</td><td>Study One:
No PE or DVT was reported. Age, BMI, and HRT were determined to not be risk factors for wound complications, fistula formation or vaginal stenosis
Study Two:
92 % of patients stopped taking hormones before surgery. 8% did not. None reported perioperative DVT.

Implications
Study One:
Hormone therapy does not need to be stopped during the perioperative period as it does not put patients at an increased risk for surgery.
Study Two:
Hormone therapy might not need to be suspended during the perioperative period.</td><td>Study One:
<u>Methodological flaws</u>: The author did not know if patients sought treatments for periop complications at another institution
<u>Inconsistency</u>: some patients were taking progesterone and spironolactone with estradiol and some were not.
<u>Indirectness</u>: none
<u>Imprecision</u>: none
<u>Publication bias</u>: none

Study Two:
<u>Methodological flaws</u>: No control over which patients would continue or stop hormone therapy
<u>Inconsistency</u>: wide variations of questions
<u>Indirectness</u>: did not directly measure rate of DVT with hormone therapy continuation
<u>Imprecision</u>: none
<u>Publication bias</u>: none</td></tr>
</table>

<table>
<tr><td colspan="6">References
Kozato, A., Fox, G. W. C., Yong, P. C., Shin, S. J., Avanessian, B. K., Ting, J., Ling, Y., Karim, S., Safer, J. D., & Pang, J. H. (2021). No venous thromboembolism increase among transgender female patients remaining on estrogen for gender-affirming surgery. The Journal of Clinical Endocrinology and Metabolism, 106(4), e1586. https://doi.org/10.1210/clinem/dgaa966
Nolan, I. T., Haley, C., Morrison, S. D., Pannucci, C. J., & Satterwhite, T. (2021). Estrogen continuation and venous thromboembolism in penile inversion vaginoplasty. Journal of Sexual Medicine, 18(1), 193-200. https://doi.org/10.1016/j.jsxm.2020.10.018</td></tr>
<tr><td>Purpose</td><td>Variables</td><td>Setting/Subjects</td><td>Measurement and Instruments</td><td>Results</td><td>Evidence Quality</td></tr>
<tr><td>Study One: To determine the risk of perioperative venous thromboembolism (VTE) in transgender patients in association with their use of hormone therapy (HT).

Study Two: To determine whether perioperative estrogen cessation affects VTE risk in patients undergoing penile inversion vaginoplasty (PIV).

Design
Study One:
Retrospective chart review

Study Two:
Retrospective pre-post study</td><td>Study One:
Primary Outcome:
To determine whether use of estrogen increase VTE risk

Secondary Outcome:
n/a

Study Two:
Primary Outcome:
To determine estrogen therapy influences VTE risk

Secondary Outcome:
Rates of wound-healing complications, including hematoma, infection, wound breakdown, skin graft loss, and granulation tissue</td><td>Study One:
Setting: Mount Sinai Center for Transgender Medicine and Surgery between November 2015 and August 2019

Subjects: 919 transgender and gender nonbinary surgical patients undergone 1396 unique cases

Study Two:
Setting: Align Surgical Associates Incorporated in San Francisco, CA

Subjects: 178 transgender patients who had undergone PIV from 2014 to 2019</td><td>Study One: Standard t-test for continuous variables and chi-square test for categorical variables. Statistical significance was P < .05. SAS 9.4 was used for analysis.

Study Two: Statistics were performed with Excel and SPSS. Continuous variables were compared using Student’s t-tests. Statistical significance was set at P < .05.</td><td>Study One: One VTE event recorded in the study. None was recorded for the group that continued HT throughout the perioperative period.

Study Two:
Rates of VTE were not statistically different between the 2 groups. 0.0% vs 1.6%, P = .166

Implications
Study One:
Factors such as time on HT, preoperative management to HT were not predictive of a perioperative VTE.

Study Two:
Transgender patients undergoing PIV are not at increased risk for periop VTE when estrogen is continued.</td><td>Study One:
Methodological flaws: Patients were not randomly assigned to different groups but were separated due to a change in the policy at the hospital. Single institution study.
Inconsistency: none
Indirectness: none
Imprecision: Patients were on different types and dosages of HT.
Publication bias: none

Study Two:
Methodological flaws: small sample size. It was not known if other HT such as progesterone and antiandrogen were also being taken.
Inconsistency: none
Indirectness: none
Imprecision: none
Publication bias: none</td></tr>
</table>

References

Boskey, E. R., Taghinia, A. H., & Ganor, O. (2019). Association of surgical risk with exogenous hormone use in transgender patients: A systematic review. *JAMA Surgery*, *154*(2), 159. https://doi.org/10.1001/jamasurg.2018.4598

Haveles, C. S., Wang, M. M., Arjun, A., Zaila, K. E., & Lee, J. C. (2021). Effect of cross-sex hormone therapy on venous thromboembolism risk in male-to-female gender-affirming surgery. *Annals of Plastic Surgery*, *86*(1), 109.

Purpose/Objectives	Search Strategy	Number and Type of Studies in the Review Including Sample Sizes	Results	Conclusions/ Implications	Evidence Quality
Study One: To determine the risk factors associated with continuing cross-sex hormone treatment in the perioperative period **Study Two:** To survey the evidence on the rate of VTE in male to female transgender patients on cross sex hormone therapy when undergoing surgeries	**Study One:** Databases are PubMed and Excerpta Medica. Search terms: testosterone, estrogen, estradiol, oral contraceptive, spironolactone, cyproterone acetate, finasteride, dutasteride, leuprolide, goserelin, and histrelin, surgery, perioperative, thrombosis, thromboembolism, and operative. Limits: inception to 2018 Reviewers: 2 authors (E.R.B. and O.G.) **Study Two:** Author did not disclose the search strategy	**Study One:** 18 articles were found. One was a randomized clinical trial, 11 were cohort studies and 6 were case-control studies. There were 15,308 participants in total. **Study Two:** 7 studies. One case-control study. One case review study. Five retrospective studies. There were 1500 patients in total.	**Study One:** One study showed that transgender patients taking testosterone were more likely to experience hematoma after surgery but the difference was not significant. Another study on cisgender men showed no increased surgical risk with testosterone. Studies on estrogen use in cisgender women were inconclusive with some having an increased risk and some do not. There were mixed results on other drugs used in cross-sex hormone therapy as well. **Study Two:** Average rate of VTE across studies was 2.6%	**Study One:** Management of hormone therapy should be individualized based on risk factors as there is insufficient evidence to recommend suspension or continuation during the perioperative period. **Study Two:** Not enough data to determine increased VTE risk when patients continue or suspend hormone therapy prior to surgery.	**Study One:** Methodological flaws: the search was not limited to the transgender population Inconsistency: none Indirectness: the literature is inconclusive and does not provide a standard of care Imprecision: none Publication bias: none **Study Two:** Methodological flaws: No mention of search strategy Inconsistency: lack of uniformity in the type of surgery Indirectness: the literature is inconclusive and does not provide a standard of care Imprecision: none Publication bias**:** none

References

Nolan, B. J., & Cheung, A. S. (2020). Estradiol therapy in the perioperative period: Implications for transgender people undergoing feminizing hormone therapy. *The Yale Journal of Biology & Medicine, 93*(4), 539-548.

Kotamarti, V. S., Greige, N., Heiman, A. J., Patel, A., & Ricci, J. A. (2021). Risk for Venous Thromboembolism in Transgender Patients Undergoing Cross-Sex Hormone Treatment: A Systematic Review. *The journal of sexual medicine, 18*(7), 1280–1291. https://doi.org/10.1016/j.jsxm.2021.04.006

Purpose/Objectives	Search Strategy	Number and Type of Studies in the Review Including Sample Sizes	Results	Conclusions/ Implications	Evidence Quality
Study One: To review the literature that has been conducted on VTE risk in the perioperative period for patients being treated with estradiol with a focus on transgender population. **Study Two:** To evaluate the rate of VTE among transgender individuals on hormone therapy and compare it to that of the cisgender population.	**Study One:** Peer reviewed journals within PubMed from January 1970 to February 11, 2020. Search terms: estradiol, estrogen, thrombosis, thromboembolism, surgery, perioperative. **Study Two:** Database: PubMed, Google Scholar, Conchrane and EBSCO. Search terms: gender dysphoria, transgender, transexual, thrombosis, thromboembolism, anticoagulation. Limits: Absence of follow up. English Language. Review articles, Case Report. Reviewers: Not mentioned	**Study One:** VTE in trans individuals undergoing hormone therapy: 14 studies. 7 retrospectives. 4 prospective. 2 cross sectionals. 1 electronic medical record-based study 5798 subjects VTE risk by estradiol formulation: 8 studies. 4 case-control. 2 cohort. 2 matched cohort. 1,920,835 subjects Perioperative VTE with estradiol treatment: 12 studies. 6 case control. 4 prospective cohort. 2 retrospective cohort. 712 subjects. **Study Two:** 22 studies in total, 11 reporting VTE in the transgender population (9,180), 6 in cis-female (18,748), and 5 in cis-male (84,965) patients. Combination of retrospective, survey, and prospective studies.	**Study One:** For VTE rate among transgender individuals, results vary. However, there was a lack of consistency among dose, route, and cessation time of estradiol treatment. **Study Two:** Weighted averages for VTE occurrence were calculated from pooled data. The rate of VTE was found to be higher in AMAB patients when compared to AFAB patients (42.8 vs 10.8 per 10,000 patient years, p=.02). The rate of VTE in AMAB is similar or higher than cis-female. AFAB is similar to the cis-male.	**Study One:** Current guidelines recommend withholding estradiol 2 to 4 weeks prior to surgery. However, there are limited evidence that have shown an increased risk of VTE in transgender individual undergoing hormone therapy. More studies are needed to develop an evidence-based guideline for hormone therapy management in the perioperative period. **Study Two:** Unable to quantify perioperative VTE risk due to the lack of data provided in which patients continued HRT throughout the perioperative period. Further research is needed to assess the safety of continuing hormone therapy in the perioperative period.	**Study One:** Methodological flaws: only one database was used. Inconsistency: lack of consistency in intervention. Variable population Indirectness: inconclusive evidence Imprecision: none Publication bias: none **Study Two:** Methodological flaws: Not directly addressing patients undergoing surgery. Based on retrospective studies with significant heterogeneity. Inconsistency: The hormone regimens were not controlled. Indirectness: Inconclusive evidence Imprecision: Lack of available data addressing the transgender population specifically. Publication bias**:** none

<table>
<tr><td colspan="6">References
Fourie, A., Ahtiala, M., Black, J., Hevia, H., Coyer, F., Gefen, A., LeBlanc, K., Smet, S., Vollman, K., Walsh, Y., & Beeckman, D. (2021). Skin damage prevention in the prone ventilated critically ill patient: A comprehensive review and Gap Analysis (PRONETECT study). Journal of Tissue Viability, 30(4), 466–477. https://doi.org/10.1016/j.jtv.2021.09.005
Thompson, A., Brennan, K., Cox, A., Gee, J., Harcourt, D., Harris, A., Harvie, M., Holen, I., Howell, A., Nicholson, R., Steel, M., & Streuli, C. (2008). Evaluation of the current knowledge limitations in breast cancer research: A gap analysis. Breast Cancer Research, 10(2). https://doi.org/10.1186/bcr1983</td></tr>
<tr><td>Objective/Purpose</td><td>Variables/Metric/Forms of Data</td><td>Setting/Participants</td><td>Measurement and Instruments</td><td>Results</td><td>Evidence Quality</td></tr>
<tr><td>Study One:
To identify and review proning and skin care guidelines

Study Two:
To determine which area of breast cancer research would produce the greatest impact on patients</td><td rowspan="2">Study One:
Comprehensive search was done from Medline on the PubMed interface, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO interface), Cochrane Database of Systematic reviews and The Cochrane Central Register of Controlled Trials up to July 2021

Study Two:
Seven key research areas were selected for review: Genetics of breast cancer; Initiation of breast cancer; Progression of breast cancer; Therapies and targets in breast cancer; Disease markers in breast cancer; Prevention of breast cancer; Psychosocial aspects of breast cancer</td><td rowspan="2">Study One:
Ghent University in Ghent, Belgium. .
Expert consultation (two experts were from the United States of America, three from Belgium, and one expert each were from Chile, Canada, Finland, Israel, Australia, and South Africa.)

Study Two:
56 Breast Cancer Campaign grant holders and prominent UK breast cancer researchers</td><td rowspan="2">Study One:
Gap analysis.
Appraisal of Guidelines for Research and Evaluation (AGREEII) instrument to evaluate guidelines

Study Two:
Participants presented summaries on their assigned theme.
Questions for all themes: What do we know? What are the gaps? Problems. Translational implication. Recommendations</td><td>Study One:
A total of 24 guideline documents were identified: seven from the literature review and 17 from organizations.

Study Two:
Seven gaps were identified. Barriers to progress were lack of financial and practical resources and poor collaboration between disciplines</td><td rowspan="2">Study One:
Methodological flaws: study was not done directly to address effectiveness of gap analysis
Limitations: guidelines from hospital are mainly posted on their intranet and not available to the public
Coherence: did not specify who were the experts
Adequacy of Data: did not specify experts
Relevance: data support use of gap analysis
Publication Bias: none

Study Two:
Methodological flaws: study was not done directly to address effectiveness of gap analysis
Limitations: none were mentioned
Coherence: did not specify experts
Adequacy of Data: adequate
Relevance: data support use of gap analysis
Publication Bias: none</td></tr>
<tr><td>Design & Sampling Strategy
Study One:
Gap analysis

Study two:
Gap analysis</td><td>Implications
Study one:
The gap analysis provided the basis for a education and training program for skin care in the prone patient.
Study two:
More funding is needed to target these gaps.</td></tr>
</table>