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HORMONAL CONTRACEPTION AND MENOPAUSAL HORMONE THERAPY: A REVIEW OF PERIOPERATIVE CONSIDERATIONS FOR ORTHOPAEDIC SURGEONS

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BACKGROUND: Exogenous estrogen is a double-edged sword in the realm of orthopaedic surgery, providing many musculoskeletal health benefits to menopausal women yet adding an additional risk of venous thromboembolism (VTE) in the perioperative setting for patients using certain forms of hormonal contraception and menopausal hormone therapy (MHT). The primary objective of this review is to summarize the known literature regarding the VTE risks of perioperative medications containing exogenous estrogen among orthopaedic patients. A secondary objective is to provide guidance to orthopaedic surgeons regarding perioperative management of commonly encountered forms of hormonal contraception and MHT.
METHODS: A summative review of existing literature regarding VTE risk of various forms of hormonal contraception and MHT is provided, with emphasis on perioperative VTE risk surrounding major and minor orthopaedic surgery.
RESULTS: Increased risk of VTE has been identified after arthroscopic knee procedures in patients utilizing oral contraceptive pills and after major lower extremity surgery in patients using MHT, yet there is not a clear standard of care as to how to manage these medications after surgery or how and when to adjust VTE prophylaxis. Regardless of the mode of delivery (pills, patches, vaginal rings), hormonal contraception with exogenous estrogen carries some associated VTE risk that can be compounded by surgery. Depo-Provera has also demonstrated increased risk. Forms of hormonal contraception without elevated VTE risk are progestin only pills and intrauterine devices (IUDs) as well as Nexplanon. MHT with systemic level doses of exogenous estrogen delivered orally has associated VTE risk. While systemic transdermal and transvaginal formulations of estrogen have not been shown to increase VTE risk in the non-surgical state, the risk when combined with the perioperative state after major operations is not yet known. Local estrogen therapies for vaginal symptoms of menopause do not increase risk of VTE.
CONCLUSION: Given the frequent utilization of hormonal contraception and MHT, orthopaedic surgeons should consider the use of medications containing exogenous estrogen in the perioperative VTE risk assessment of patients. Further discussion toward the perioperative management of these medications and standardization of care for patients with increased VTE risks should be encouraged.

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INTRODUCTION

Over a century ago, Rudolf Virchow described three factors contributing to venous thrombus: endothelial injury, stasis, and hypercoagulability.[1] Most orthopaedic surgeries inherently involve endothelial injury and venous stasis, as well as hypercoagulability due to the systemic response to surgery and possible pre-existing risk factors like smoking, obesity, cancer, and medications. The use of exogenous estrogen, a component of combined hormonal contraceptives (CHC) or menopausal hormone therapy (MHT), is associated with increased venous thromboembolism (VTE) risks.[2-4] Since the orthopaedic patient population includes females of reproductive, perimenopausal, and postmenopausal age, perioperative VTE risk assessment should comprehensively review the use of estrogen-containing medications.

CHC and MHT are offered in many local and systemic formulations and modes of delivery, including oral, transdermal, and transvaginal options. CHCs of higher doses and combined with specific progestin derivatives have been reported to confer greater VTE risk.[5-7] Specifically, CHC containing 50ug estrogen had greater VTE risk as compared to those with less than 35ug, and those containing over 30ug had greater VTE risk than those with 20ug.[8-10] CHCs with the progestin drospirenone carry a higher risk of thrombosis than those with levonorgestrel.[6] Risk-benefit discussions are therefore warranted in the context of hormonal therapy. In addition to roles in contraception and menopausal symptom management, exogenous estrogen reduces risk of osteoporosis and fragility fractures in post-menopausal women, a significant population within orthopaedics.[11]

Here we provide a summative review of existing literature regarding perioperative VTE risk in orthopaedic surgery among patients taking medications containing exogenous estrogen. The purpose of this review is to (1) summarize the current literature on the risks of perioperative CHC and MHT in orthopaedic patients and (2) provide guidance for VTE risk assessment, prophylaxis, and perioperative medication management.

VENOUS THROMBOEMBOLISM IN ORTHOPAEDIC PATIENTS

The risk of deep venous thrombosis (DVT) or pulmonary embolism (PE) associated with postoperative hypercoagulability is widely present in the orthopaedic patient population. The National Institute for Clinical Excellence guidance for reducing VTE risk among inpatients undergoing surgery suggests the use of both mechanical and pharmacological prophylaxis for orthopaedic patients and those with additional risk factors.[12,13] While VTE incidence ranges from 10% to 40% in hospitalized general surgery patients without prophylaxis, asymptomatic VTE incidence ranges up to 40% to 60% in untreated patients undergoing major orthopaedic surgery, further indicating that attempts to reduce risk factors are imperative.[14]

Examples of major orthopaedic surgery include lower extremity joint reconstruction and operative fracture management of long bones of the extremities or pelvis, while non-major orthopaedic procedures may include joint arthroscopy, hand surgery, or foot surgery. In a case control study of 9146 patients who underwent anterior cruciate ligament reconstruction, which may be considered non-major, there was a 0.5% incidence of DVT within 30 days postoperatively, close to the 0.53% incidence of VTE complications reported in an epidemiological study of upper extremity arthroplasties.[15,16] These rates contrast with those of lower extremity arthroplasty, fracture, and spine surgery, with an in-hospital VTE rate of 0.59% after total hip arthroplasty, 1.03% after total knee arthroplasty, one-month symptomatic VTE incidence of 1.7% for hip fracture, 2.4% for femur fracture, and 1.1% for tibia-fibula fracture, and as high as 13% for postoperative asymptomatic VTE in spine patients, as reported in the available literature.[17-19] While ACL reconstruction may be considered non-major, there are many other sports medicine-related procedures or procedures performed by sports medicine specialists that could fall under the category of major procedures, such as multiligament knee reconstruction, periarticular knee osteotomies, proximal humerus fracture fixation, or shoulder arthroplasty.

Although the risk of VTE is lower in non-major orthopaedic procedures, risks are certainly exacerbated in patients with additional hypercoagulable characteristics.[19] Specific VTE risk factors previously identified among orthopaedic patients include older age, history of previous VTE, malignancy, inherited hypercoagulable

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conditions, and use of oral contraception.[20-22] Pediatric orthopaedic patients are described to have higher VTE risk in the setting of cancer, obesity, or oral contraceptive use.[20] Exogenous estrogen in the form of CHC is therefore widely accepted as a VTE risk factor.

Research into the use of CHC among orthopaedic patients has typically assessed those undergoing non-major surgery. Hormonal contraceptive use remains the most frequent VTE risk factor in fertile women receiving non-major orthopaedic surgery, although some studies report this additional risk as insignificant.[21] For example, oral contraceptives at the time of shoulder arthroscopy was not associated with an increased VTE risk.[23] In a separate cohort of patients undergoing hip arthroscopy, a low incidence of symptomatic postoperative VTE was reported, with neither gender nor oral contraception as significant risk factors.[24] However, a recent study analyzing over 64,000 patients reported an increase in symptomatic DVT and PE among knee arthroscopy patients taking oral contraceptives and an increased DVT risk among knee arthroscopy and anterior cruciate ligament reconstruction (ACLR) patients taking oral contraceptives.[25] In a 2021 survey of 94 orthopaedic surgeons who routinely perform ACLR, only 40% always inquire about hormonal contraceptive medications. Surgeons who asked about hormonal contraceptive use and subsequently changed their VTE prophylaxis plan were more likely to be women (OR 4.2, p=0.01; OR 2.8, p=0.02, respectively) or more likely to have had female patients with VTE after ACLR (OR 2.9, p=0.03; OR 4.6, p=0.001, respectively).[26] Research on VTE risk in the setting of contraceptive use in patients undergoing major orthopaedic surgeries is lacking but warranted.

Exogenous estrogen use in the form of MHT is also prevalent among orthopaedic patients, especially given the pathogenesis of osteoporotic fractures among postmenopausal women. A New Zealand study reported a two- to four-fold increase in VTE risk among surgical patients taking MHT.[27] However, MHT may provide some clinical benefit to bone health by aiding in fracture healing and preventing fragility fractures.[28-30] In joint reconstruction, MHT use is associated with a 40% reduction in revision after total knee or hip arthroplasty.[31] As MHT is protective against osteoporosis, the musculoskeletal benefits of MHT are likely also relevant to procedures like rotator cuff repair, in which osteoporosis is known to be associated with failure of healing.[32,33]

While the efficacy of pharmacological VTE prophylaxis after major orthopaedic surgery is well-supported, certain patient characteristics and clinical indications should direct more personalized perioperative management of VTE prophylaxis and other medications contributing to overall VTE risk.[34,35] Despite the evidence of oral contraception as a significant VTE risk factor and the suggestion of benefit with MHT, we continue to lack consensus regarding the perioperative management of different forms of exogenous estrogen, progestogens, and modes of delivery. A better understanding of these medications and their impact on patient safety is necessary for the development of appropriate guidelines for VTE prophylaxis modification in these patient populations.

HORMONAL CONTRACEPTION

Hormonal contraception (HC) is used by over 80% of women during their reproductive years.[36,37] Despite the introduction of other formulations, oral contraceptive pills remain the most popular hormonal contraceptive among U.S. women. Currently, two-thirds of women aged 15-49 use contraception. The most common contraceptive methods are female sterilization (18.1%), oral contraceptive pills (14.0%), followed by long-acting reversible (hormonal) contraceptives (10.4%).[37]

Given the various compositions and formulations, each hormonal contraceptive is associated with different thromboembolism risks. Hormonal contraceptive types, including pills, patches, rings, intrauterine devices (IUDs), injections, and implants, are categorized by their associated VTE risk in Table 1.

Oral Contraceptive Pills

Oral contraceptive pills include both combined oral contraceptives (COCs) and progestin-only pills (POPs); the former contains estrogen and a progestin. The principal estrogen component of COCs is ethinyl estradiol with doses ranging 10-50ug. The progestin component is available in different generations, varying in their androgenic effects.[38]

Given their different components, COCs and POPs carry unique clotting risks. While COCs as pills,

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patches, and rings have a known thromboembolic risk among otherwise healthy women, first and second generation progestins do not convey additional VTE risk.[38,39] Current literature suggests that this risk is primarily associated with estrogen and is dependent upon dosage and duration.[40] Simultaneously, some progestins, particularly those of the third generation such as desogestrel, appear to modulate the estrogenic effect, increasing VTE risk.[41,42] Overall, the relative risk of VTE in women using COCs is higher as compared to non-users.[43] Furthermore, this risk changes by duration, with reported relative risk from a historical national registry cohort study being highest at 4.25 in the first year of use, 3.07 between 1 and 4 years, and 2.71 over 4 years, as compared to VTE in non-users.[43] Although POPs may not carry an additional VTE risk, patients must adhere to strict dosing to ensure contraceptive efficacy.

Table 1. Types of hormonal contraception (HC) and associated venous thromboembolism (VTE) risk in the general population[38,39]

Risk of VTE	*HC Type by Route*	*Generic Composition*	*Brand Name Examples*
Increased	COCs	Norethindrone acetate + ethinyl estradiol	Junel, Loestrin
		Levonorgestrel + ethinyl estradiol	Alesse, Levlen, Lybrel, Seasonalle
		Norgestimate + ethinyl estradiol	Sprintec
		Drospirenone + ethinyl estradiol	Yaz
		Desogestrel + ethinyl estradiol	Apri
	Vaginal Ring	Segesterone + ethinyl estradiol	Annovera
		Etonogestrel + ethinyl estradiol	Nuvaring
	Transdermal Patches	Levonorgestrel + ethinyl estradiol	Twirla
		Norelgestromin + ethinyl estradiol	Xulane
	Progestin Injection	Depot medroxyprogesterone acetate	Depo-Provera
Not increased	Progestin IUD	Levonorgestrel	Kyleena, Lyletta, Mirena, Skyla
	Subcutaneous Progestin Implant	Etonogestrel	Nexplanon
	POPs	Norethindrone	Camila, Micronor, Nor-QD
		Drospirenone	Slynd

COCs, combined oral contraceptives; IUD, intrauterine device; POPs, progestin only pills

Combination Patches and Rings

Combined hormonal contraceptives as combination transdermal patches and vaginal rings carry similarly increased thromboembolism risk, when compared with COCs, presumably attributed to the presence of exogenous estrogen.[38] The patches and rings in the U.S. are listed in Table 1. The United States Medical Eligibility Criteria for Contraceptive Use (US MEC), published by the CDC in 2016, categorizes vaginal rings and patches in the same VTE risk group as COCs of similar hormone formulations[44,45], although epidemiological studies have found a higher risk of VTE with the vaginal rings and patches.[43]

IUDs

Intrauterine devices are available in both non-hormonal and hormonal forms, as their contraceptive function is both mechanical and androgenic. The non-hormonal device contains copper with no additional effect on DVT risk. Hormonal IUDs are progestin-containing and do not affect surgical VTE risk (Table 1).[43,46] For any type of surgery, all IUDs are US MEC Category 1 (no restriction for use) or Category 2 (advantages generally outweigh the theoretical or proven risks).[44]

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Implants and Injections

The subcutaneous implant, which is highly effective for up to three years, is a 4-cm rod inserted into the upper arm containing etonogestrel progestin. Although the product lists current or history of thrombosis as contraindications, the US MEC assigns it within Category 2, suggesting that the advantages, even with a DVT history, generally outweigh the risks.[44]

Depo medroxyprogesterone acetate (DMPA) is the most common injectable contraceptive, containing no estrogen and dosed at 150 mg/ml every 13 weeks. A 2016 systematic review reported several studies where the use of DMPA was associated with an increased risk of VTE.[39,44] A 2-fold increased risk was confirmed in a recent study using US private insurance claims data.[47] Providers should additionally be aware that the potential for increased VTE risk with DMPA may be compounded in patients with underlying risk factors, such as smokers, women with thrombogenic mutations, or those undergoing orthopaedic surgery requiring immobilization.[38]

Overall Risk

Among the various hormonal contraceptive formulations, oral contraceptive pills carry an absolute risk of death from PE of 10.5 per million woman-years, with the safest COC option being the combination of levonorgestrel and low-dose estrogen.[48] Regardless of the mode of delivery— pills, patches, vaginal rings— hormonal contraception with exogenous estrogen carries some associated VTE risk.[7]

Other factors, including age, obesity, and smoking, also contribute to VTE risk among women using hormonal contraception. DVT risk has been estimated to increase five-fold with increasing age and three-fold with obesity.[49-51] In a population-based study of 740 patients, VTE incidence rates increased exponentially with age, specifically in age groups over 65.[51] Body mass index (BMI) is a known thrombotic risk factor with odds ratios of 1.7 and 2.4 for BMI 25-30 and > 30, respectively, as compared to BMI < 25. In women using oral contraceptives as compared to the previous control, odds ratios for thrombosis are 11.6 and 23.8 for BMI 25-30 and > 30, respectively.[50] A recent study evaluating the effect of oral contraception on VTE risk following arthroscopy noted that patients taking COCs are twice as likely to develop VTE and four times as likely to have a VTE event with the risk factors of obesity or smoking, suggesting that the ultimate risk is more than the sum of individual risk factors.[25] Others have estimated that smoking doubles the risk of DVT independent of contraceptive use, and smoking while using COCs may confer up to an eight-fold increase in DVT risk.[52] These factors should all be taken into consideration during surgical planning for women using hormonal contraception. It is imperative that we continue to expand our understanding of the differential safety profiles to improve perioperative management of hormonal contraception and appropriate VTE risk assessment.

MENOPAUSAL HORMONE THERAPY (MHT)

Hormonal therapy targets the pathways that mediate perimenopausal vasomotor symptoms. Women may experience hot flashes, night sweats, sleep disturbances, poor concentration, and mood changes as they transition into menopause. Hormone replacement in the form of hormonal contraceptives may be the appropriate recommendation for women wanting to avoid pregnancy during their menopausal transition. Vasomotor symptoms may also be alleviated by menopausal hormone therapy (MHT), which contains lower estrogen doses as compared to hormonal contraceptives. While having declined since the publication of the principal results in 2002, the use of exogenous estrogen via systemic MHT among midlife women remains prevalent.[53] Depending on the symptoms, both systemic and local treatment options are available.

Low- and high-dose systemic MHT is categorized into estrogen therapy (ET), estrogen-progestogen therapy (EPT), and estrogen receptor agonist/antagonist therapy (ERAA). ET is available as an oral, patch, gel, vaginal ring, or spray for postmenopausal women who have undergone a hysterectomy. EPT, as a combination pill, combination patch, or estrogen patch, gel, spray or vaginal ring, with a progestogen pill, is an option for postmenopausal women with a uterus, as progestogen reduces the risk of endometrial hyperplasia and cancer associated with unopposed estrogen therapy. ERAA is a progestogen-free option for postmenopausal women with a uterus that similarly protects the endometrial lining from unopposed proliferative estrogen effects.

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Local vaginal estrogen therapy includes much lower dose topical or vaginal estrogen-containing rings, creams, and inserts, or tablets for women bothered by vaginal symptoms of genitourinary syndrome of menopause (including vaginal dryness, dyspareunia, and urinary symptoms).

The VTE risks associated with systemic MHT differ by dosage and formulation. Postmenopausal exogenous estrogen has a known increased VTE risk, which may be highest in the first year then decreased afterwards.[54,55] Clinical risk factors of older age and obesity, like those for HC, compound VTE risk in patients taking MHT.[56] The risk associated with oral estrogen is decreased in lower dosages, however. Similarly, transdermal formulations do not appear to confer an additional VTE risk in the non-surgical state. One observational study of 80,396 women aged 40-79 with VTE diagnoses suggested that transdermal MHT (estrogen only or combined, any dose) were not associated with an increased VTE risk.[57] The risk of transdermal and transvaginal MHT during the perioperative state after major operations, however, is not yet known. The differences in VTE risk between MHT options are summarized in Table 2.

Table 2. Types of menopausal hormone therapy (MHT) for management of vasomotor symptoms and associated venous thromboembolism (VTE) risk

Risk of VTE	*Formulation*	*Route/Type*	*Brand Name Examples*
Increased	Systemic	Oral conjugated equine estrogen	Premarin
	Systemic	Oral estradiol	Estrace
	Systemic	Oral esterified estrogen	Menest
	Systemic	Oral estrogen-progestogen combinations	Activella, Amabelz, Angeliq, FemHRT, Jevantique Lo, Jinteli, Mimvey, Prefest, Prempro
	Systemic	Oral estradiol-progestogen	Bijuva
	Systemic	Oral conjugated equine estrogen and bazedoxifene	Duavee
Not increased	Systemic	Estradiol patches*	Alora, Climara, Menostar, Minivelle, Vivelle-Dot
	Systemic	Estrogen-progestogen patches*	Climara Pro, Combi-Patch
	Systemic	Topical gel*	Divigel, Elestrin, Estrogel
	Systemic	Topical spray*	Evamist
	Systemic	Systemic intravaginal ring*	Femring
	Local	Vaginal ring	Estring
	Local	Vaginal tablet	Vagifem, Yuvafem
	Local	Vaginal cream	Estrace, Premarin vaginal
	Local	Intravaginal insert	Imvexxy

**While systemic transdermal and transvaginal formulations of MHT have not been shown to increase VTE risk in the non-surgical state, the risk when combined with the perioperative state after major operations is not yet known.*

In general, oral systemic MHT confers a significantly increased VTE risk, with the highest risk among oral synthetic options.[58-61] Oral MHT doubles the VTE risk in the first two years of therapy and carries higher risks if combined with a progestin (a synthetic as opposed to a natural progestogen such as progesterone).[62] Combinations with micronized progesterone

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appear to be safer with respect to thrombotic risk.[56,63]

Transdermal patches and topical or vaginal MHT have much safer VTE risk profiles. Low-dose, non-systemic vaginal MHT has a nearly negligible VTE risk.[31] Transdermal and vaginal formulations have lower risk by bypassing first-pass hepatic metabolism.[61,64,65] Route of administration alone, however, may not confer sufficient protection against VTE. A meta-analysis of seven population-based, observational studies including 26,471 VTE cases (735 users of transdermal estrogen, 3,103 users of oral estrogen, and 22,633 non-users) analyzed risk based on route, hormonal regimen, and progestogen (progesterone or progestin) type, suggesting that transdermal estrogen with norpregnane carries an increased VTE risk.[66] This result, combined with the VTE risk of perioperative states, is suggestive of an unknown potential VTE risk of transdermal MHT when used after major operations. Overall, however, transdermal, topical, and vaginal MHT confer safer risk profiles yet remain underused with an overwhelming patient preference for oral formulations.[57] Additional risk-benefit considerations for utilizing MHT are summarized in Table 3.[67] Systemic MHT increases VTE risk but confers significant risk reduction for osteoporosis and fragility fractures among post-menopausal women.

Table 3. Risk-benefit considerations in menopausal hormone therapy (MHT)[55,67,68]

Outcome	*Type of MHT**	*Benefit*	*Risk*
Venous Thromboembolism	ET		+
	EPT		+
Osteoporosis	ET	+	
	EPT	+	
Fractures	ET	+	
	EPT	+	

**ET, estrogen therapy; EPT, estrogen + progestogen therapy*

CONSIDERATIONS FOR PERIOPERATIVE PLANNING

There is limited data regarding the appropriate perioperative management of hormonal medications. A 2022 NEJM article highlighted the importance of considering adverse effects when stopping these medications perioperatively, comparing the benefit of reducing VTE risk with the potential consequences of unintended pregnancy, withdrawal bleeding, and endometrial pain, among others.[69] For continuing hormonal contraception perioperatively, the risk of an unwanted pregnancy must be weighed against the increased risk of VTE, and no current guidelines exist for adjusting medications preoperatively or postoperatively.[70] One study suggested the cessation of oral contraception four weeks prior to a major or lower limb surgery, given the increased DVT risk.[71] The risk-benefit profiles for HC and MHT have influenced our recommendations, as the contraceptive purpose of HC is inherently different than symptom control of MHT. One randomized controlled trial of MHT in women with a history of coronary heart disease but no history of VTE found a 2.7-fold increased risk of VTE in women taking MHT as compared to women not taking MHT. Results showed a further increased risk of VTE following lower extremity fracture or within 90 days of inpatient surgery in women taking MHT as compared to women not taking MHT.[72] While there are no current recommendations suggesting holding MHT preoperatively, in clinical practice, women undergoing major surgeries typically have additional clinical risk factors that require the use of VTE prophylaxis.[73,74]

Rather than withholding hormonal medication, however, higher doses or longer courses of anticoagulation have been proposed as prophylaxis for those with increased VTE risk. In women who experienced their first VTE while using exogenous estrogen, the risk of recurrent VTE was low without any additional benefit from extended anticoagulation, suggesting a limited period of additional VTE prophylaxis.[75] One study analyzing cardiovascular parameters measured

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increased C-reactive protein, increased prothrombin fragment 1 + 2, and decreased antithrombin in patients taking conventional doses of MHT. These serum markers were indicative of the hypercoagulable state induced by exogenous estrogen.[76]

In addition to considering medications, the operative VTE risk differs by procedure type, as previously defined major orthopaedic surgeries include upper and lower extremity joint arthroplasty, fractures requiring internal fixation, multiligament knee reconstructions, and periarticular knee osteotomies, while minor orthopaedic surgeries may include arthroscopic interventions like meniscus repair or ACL reconstruction. Given these considerations, we have proposed the below recommendations, graded by their supporting evidence.

The standard perioperative VTE prophylaxis in orthopaedic surgery has been outlined by the American College of Clinical Pharmacy and American Association of Orthopaedic Surgeons guidelines, among other recommendations.[77] In addition to this standard of care, orthopaedic surgeons may consider altering VTE chemoprophylaxis and withholding CHC, DMPA and oral MHT in the setting of major surgery or multiple VTE risk factors. In patients preparing for minor orthopaedic surgery and taking forms of HC or MHT without increased VTE risk, it is reasonable to prescribe VTE prophylaxis according to standard guidelines without altering hormonal medications.[78] After reviewing the available literature, the current practice consensus from our orthopaedic, women's health, and hematology authors, with respect to managing HC and MHT associated with increased VTE risk, is delineated in Figure 1. Due to a paucity of studies regarding perioperative VTE prophylaxis in patients taking hormonal therapy, there is no established standard of care. However, we view these suggestions as a general framework for individualized decision-making that encourages collaboration with other providers, especially those managing hormonal medications. Additionally, risks of neurologic compromise or retroperitoneal bleeding from anticoagulation for certain surgical procedures, including spine surgery, must be weighed against the risks of VTE in patients taking hormonal therapy.

Considerations for perioperative management include a combination of increasing VTE chemoprophylaxis and withholding hormonal contraceptives or MHT. All patients should be notified of their respective VTE risks and educated about clinical signs of VTE. Providers may consider suggesting that patients schedule primary care or gynecologic follow-up for additional hormonal contraceptive and MHT adjustments. Patients should be advised to use non-hormonal, back-up contraceptive methods or hormonal methods that do not increase the risk of thrombosis if their hormonal contraception is adjusted or discontinued.[40] There are also non-hormonal options for the management of MHT.[79] Collaboration with women's health providers regarding hormonal medications is encouraged for appropriate perioperative risk reduction.

Additionally, patients using exogenous estrogen who have sustained a traumatic injury leading to prolonged preoperative immobilization may have a baseline higher VTE risk. A post-traumatic, presurgical DVT may delay surgical intervention and warrant medication management to lower further VTE risk perioperatively. More specifically, patients should be counseled to discontinue CHC, DMPA, and oral MHT medications when a VTE is identified. In the setting of an identified perioperative VTE, orthopaedic providers should collaborate with women's health and hematology to determine the most appropriate surgical and medical optimization.

Transgender women are another population of patients who take medications containing exogenous estrogen. A shared decision-making process including the patient's tolerance for withholding gender-affirming hormone therapy, associated VTE risk based on surgical procedure, and other patient-specific risks should be considered when determining perioperative VTE prophylaxis and medication management.

CONCLUSION

The prevalence of hormonal contraception and MHT use in the perioperative period is high amongst the orthopaedic patient population, including younger patients with sports-related injuries as well as older patients with arthritis, fractures, and rotator cuff tears. While there are important benefits of these medications including contraception, menopausal symptom management, and reduced risk of osteoporosis and fractures, the known increase in VTE risk in some

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formulations cannot be ignored. More surveys of current practice patterns may be helpful to determine the differences between orthopaedic subspecialties that treat patients of varying ages and comorbidities. Additionally, increasing awareness about the compounded risk of perioperative VTE as it relates to hormonal medications is crucial. Clearly more research, particularly a noninferiority trial, is needed, as suggested in the recent NEJM article highlighting the increased VTE risk and its impact on perioperative management options.[69]

After summarizing the current literature on VTE risk by type of exogenous estrogen, we have proposed general recommendations for perioperative consideration. We hope to encourage further discussion toward a more evidence-based standardization of care for women undergoing orthopaedic procedures. While the decision-making model of our current practice patterns delineates a general framework, a better understanding of the compounded VTE risk is necessary to optimize patient outcomes. Our review aims to highlight this lack of standardization and provide insight into a more unified consensus between providers who prescribe hormones and those who operate.

Recommendations for Perioperative HC and MHT Management

- ◊ Orthopaedic surgeons should consider the use of HC and MHT in the perioperative VTE risk assessment of patients undergoing minor and major orthopaedic surgeries. (Grade B)
- ◊ Postoperative VTE prophylaxis need not be altered in the setting of HC or MHT that do not increase VTE risk (Tables 1 and 2) (Grade B)
- ◊ Consider altering postoperative VTE chemoprophylaxis in the setting of HC or MHT that increase VTE risk (Tables 1 and 2) (Grade B)
- ◊ Prior to major orthopaedic surgery or in the setting of multiple VTE risk factors, consider withholding HC or MHT that increase VTE risk (Tables 1 and 2) (Grade B)

JBJS Grade of Recommendation

Grade B: Fair evidence (Level II or III studies with consistent findings) for or against recommending intervention.

Figure 1. Recommendations for perioperative management of VTE prophylaxis in orthopaedic patients taking HC or MHT[80]
VTE, venous thromboembolism; HC, hormonal contraception; MHT, menopausal hormone therapy; JBJS, Journal of Bone and Joint Surgery

Conflicts of Interest
The authors declare no conflicts of interest with the contents of this study.

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