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PERSPECTIVES

# Contraception in Medically Complex Adolescents and Young Adults

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**Abstract:** Contraception is a significant part of comprehensive sexual and reproductive health (SRH) care for adolescents and young adults (AYA). While providers may assume that AYA with chronic illness are not sexually active, studies have shown that there are no differences in their sexual practices compared to their counterparts without an illness. This assumption may result in less SRH screening, preventative services, and counseling by providers resulting in decreased basic sexual knowledge, increased risk of unplanned pregnancy, and other health disparities. Sexually active AYA with medical complexity are particularly in need of contraception for a variety of reasons. A better understanding of the complexities around contraception counseling can help increase utilization rates, improve shared-decision making around family planning, and reduce the stigma around sexual health counseling in this population. We have included three sections. First, a general overview of contraception methods. Next, an overview of contraceptive methods currently available, their efficacy, and medical eligibility criteria for their use in AYA who have certain characteristics or medical conditions. Finally, cases adapted from real clinical scenarios to highlight specific recommendations for contraception in AYA women living HIV, autoimmune conditions, and those who have received a solid organ transplant. This information will help providers to consider the multiple factors that influence contraception decision-making (including clinical status, thrombosis risk, medication interactions, safety), and optimize care for AYA living with chronic illness.

**Keywords:** adolescent, young adult, contraception, sexual health, chronic illness

## Introduction

Contraception plays a significant role in comprehensive sexual and reproductive health (SRH) care for adolescents and young adults (AYA). While providers may assume that AYA with chronic illness are not sexually active, studies have shown that there are no differences in their sexual practices compared to their counterparts without an illness.[1–3] This assumption may result in less SRH screening, preventative services, and counseling by providers resulting in decreased basic sexual knowledge, increased risk of unplanned pregnancy, and other health disparities. Sexually active AYA with medical complexity are particularly in need of contraception for a variety of reasons such as 1) exposure to teratogenic medications, 2) concern for high-risk pregnancies due to co-morbidities associated with their chronic illness, and 3) not desiring pregnancy at this stage of their life.

Key discussion topics to include when counseling AYA include consent and boundaries, screening regarding sexually transmitted infections (STIs), human papillomavirus (HPV) vaccination, cervical cancer screening, and additional interventions such as pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) in efforts to reduce human immunodeficiency virus (HIV) transmission.[4] Providers should revisit these topics regularly. If subspecialty providers are not comfortable with initiating discussion or counseling about contraception, referral to primary care providers or specialists (such as Adolescent Medicine specialists or pediatric gynecologists) familiar with SRH guidelines for this population is imperative.

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Medically complex AYA are often on multiple medications for maintenance therapy that can be teratogenic as well as lead to other co-morbidities including hyperlipidemia, hypertension, and diabetes. Drug–drug interactions between contraceptives and other chronically used medications can result in increased drug toxicity, unintended pregnancy, and morbidity. Contraceptive failure because of pharmacokinetic interactions of co-medication is a significant concern when counseling about contraception options.

In cases where an AYA does become pregnant, options counseling should include the possibility of continuing the pregnancy, terminating the pregnancy, or creating an adoption plan. In adolescents with chronic diseases, the risks and benefits of each option should be a focus of the discussion as their pregnancies are often considered high risk and can cause increased health risks for the AYA and/or the fetus.

## Overview of Contraceptive Methods

The contraceptive methods that will be discussed in this paper can be broadly divided into non-hormonal (barrier methods, vaginal contraceptive gel, and copper intrauterine device (IUD)), combined estrogen/progestin, progestin only, and emergency contraception categories (Table 1). Availability and accessibility of methods vary by country and region of the world. Contraindications to the use of combination estrogen-progestin medications are presented in Box 1. A medical, reproductive/sexual, social, and family history will identify unacceptable health risks or relative contraindications to use of the various methods available. Table 1 outlines contraceptive failure rates based on perfect and typical use. This information should, be incorporated when counseling on the various methods, in addition to eliciting patient priorities (eg, anemia, acne, dysmenorrhea), preferences (eg, ease of use, route of administration cost, confidentiality), and potential barriers to adherence (eg ability to take medication daily)

The World Health Organization has published evidence-based guidelines outlining medical eligibility criteria for contraceptive use (WHOMEC).[5] These guidelines provide recommendations intended to help health care providers determine the safety of the initiation or continuation of contraceptive options based on factors such as medical conditions, medication use, and other personal characteristics (eg, history of smoking). Each medical condition or factor is classified into one of four numbered categories. Category 1 comprises conditions in which there is no restriction for use of a contraceptive method. Category 2 includes conditions for which the benefit of using a contraceptive method

**Table 1** Contraceptive Failure Rates

| Contraception Method | Recommended Frequency of Use | Perfect Use | Typical Use |
|---|---|---|---|
| Barrier methods | At every sexual encounter | | |
| Male condom | | 2% | 13% |
| Female condom | | 5% | 21% |
| Spermicide | | 16% | 21% |
| Vaginal contraceptive gel | | 7% | 14% |
| Combined hormonal and progestin only oral contraception | Every day at the same time | 0.3% | 7% |
| Transdermal contraceptive patch | Weekly | 0.3% | 7% |
| Vaginal ring | Monthly | 0.3% | 7% |
| Injectable depot medroxyprogesteroneacetate | Every 13–15 weeks | 0.2% | 4% |
| Subdermal implant | Up to 4 years | 0.1% | 0.1% |
| Levonorgesetrel-containing intrauterine device | 3–8 years | 0.1–0.3% | 0.1–0.4% |
| Copper intrauterine device | 10–12 years | 0.6% | 0.8% |

**Notes**: Data from: https://www.guttmacher.org/fact-sheet/contraceptive-effectiveness-united-states; https://hcp-phexxi.com/efficacy_and_safety. Typical Use: Inconsistent or incorrect usage. Perfect use: Use method as prescribed and correctly.

**Box 1** Contraindications to Use of Estrogen Containing Contraception

| |
|---|
| Severe hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg* or systolic ≥160 mmHg or diastolic ≥100 mmHg**) or vascular disease |
| Complicated valvular disease (pulmonary hypertension, risk for atrial fibrillation, history of subacute bacterial endocarditis) |
| Migraine headaches with aura |
| Specific Liver Diseases (cirrhosis, hepatocellular adenoma or malignant hepatoma) |
| Women aged ≥35 years who smoke ≥15 cigarettes per day |
| Venous thromboembolism<br>History of thromboembolism not receiving anticoagulation<br>History an acute embolic event |
| Breast cancer |
| Complicated solid organ transplant |
| Diabetic nephropathy/retinopathy/neuropathy |

**Notes**: Data from Curtis KM, Tepper NK, Jatlaoui TC, et al. US Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016; 65:1. Medical eligibility criteria for contraceptive use. Fifth Edition. World Health Organization. 2015 www.apps.who.int/iris/bitstream/handle/10665/181468/9789241549158_eng.pdf;jsessionid=0F5BCF5FB640060B05CD47F1AF197A2E?sequence=1. *per Centers for Disease Control and Prevention recommendations. **Per World Health Organization recommendations.

outweighs the risks. Conditions that fall within category 3 indicate that careful clinical judgment should be used as the theoretical or proven risks usually outweigh the advantages of using the method. For these conditions, use of the contraceptive method is usually not recommended unless more appropriate methods are not available. Finally, Category 4 indicates conditions which represent an unacceptable health risk if contraceptive method is used. The WHO continues to update recommendations as new evidence emerges to serve as a reference for policy makers, family planning organizations and national governments developing their own guidelines. The United States (US Medical Eligibility Criteria for Contraceptive Use published by the Centers for Disease Control and Prevention)[6] as well as the United Kingdom (the UK Medical Eligibility Criteria for Contraceptive Use)[7] are both countries that adapted WHO MEC criteria for their own use. It is important to note that there are changes between these adaptations from the WHO MEC including recommendations for medical conditions not covered by the WHO and removal of other recommendations for methods currently not available in the country.

# Non-Hormonal Methods

## Condoms

Correct and consistent use of latex or non-latex synthetic condoms have added benefit of reducing the risk of HIV and STI transmission. Condoms made of animal membranes such as lambskin are less elastic than latex condoms, making them less effective in STI prevention but still helpful for pregnancy prevention.[8] An additional form of contraception should be used in conjunction with barrier methods until pregnancy is desired.

## Vaginal Contraception Gel

The contraceptive gel prevents pregnancy by lowering the pH of the vagina thus impairing the motility of sperm.[9] It should be inserted into the vagina no more than one hour prior to intercourse and can be repeated before each sexual encounter. It can be used in combination with other methods (except the vaginal ring) to increase efficacy.

## Copper IUDs

This method induces a sterile inflammatory reaction impairing sperm motility which impairs both fertilization and implantation. Copper IUDs have no impact on ovulation.

# Hornomal Methods

## Combined Estrogen/Progestin Containing Methods

Estrogen suppresses follicle-stimulating hormone (FSH), inhibiting follicular development. Progestin inhibits the luteinizing hormone (LH) surge which suppresses ovulation.[10] Additionally, it thickens the cervical mucus making it less penetrable to sperm, impairs fallopian tube motility, and causes thinning of the endometrium.[10] Common side effects of these methods include nausea, breast tenderness, and bloating. They can either be used cyclically to induce regular withdrawal bleeds or continuously to suppress menses.

## Combined Hormonal Oral Contraceptive Pills (CHCs)

The most common estrogen used in CHCs is ethinyl estradiol with doses ranging from 10 mcg to 50 mcg per pill. The ethinyl estradiol is combined with various progestins. CHCs come in monophasic (all active pills have same dose of hormones) and triphasic formulations (dose of hormone varies by week). Ideally, CHCs should be taken at the same time every day to maintain suppression of ovulation to minimize the chance of pregnancy.

## Transdermal Contraceptive Patch

The transdermal patch comes in two formulations 1) 150 mcg norelgestromin and 35 mcg ethinyl estradiol and 2) 120mcg levonorgestrel and 30mcg ethinyl estradiol. The patch is changed once weekly and can be placed on the lower or upper back, lower abdomen, buttocks, or upper outer arm. This method may not be as effective in women weighing more than 198 pounds (90kg), as studies have shown the potential for incomplete ovarian suppression, secondary to variability of absorption of the active drug.[11,12] The transdermal patch should not be used in patients with a body mass index (BMI) $\geq$30 kg/m$^2$ due to concern for increased venous thromboembolism (VTE) risk.[13]

## Vaginal Ring

There are two formulations of the ring available. One contains 15 mcg of ethinyl estradiol and 120 mcg of etonogestrel and a new ring is inserted every 21 days with a 7-day ring free period. This ring can be removed from the vagina for up to three hours without a decrease in efficacy. If the ring remains out of the vagina for >3 hours, a backup method should be used.[14] The second vaginal ring contains 17.4mg ethynyl estradiol and 103mg segesterone and can be reused for an entire year. It is inserted for 21 days and then removed for 7 days for 13 cycles a year. The ring can be removed from the vagina for up to 2 hours cumulatively over the 21 days without a decrease in efficacy. If the ring remains out of the vagina for >2 hours, a backup method should be used.[15]

## Combined Injectable Contraception (CIC)

Although a combined method of injectable contraception is no longer available in some countries including the United States, CICs continue to be used in other parts of the world. CICs are composed of an estradiol ester and a long-acting progestin (eg, hydroxyprogesterone caproate (250 mg) and estradiol valerate (5 mg)). The estrogen component often results in a more favorable bleeding pattern compared to injectable progestin-only methods.[16] They are administered monthly through an intramuscular injection in the buttocks, anterior thigh, or deltoid muscle. Due to their parenteral administration CICs bypass the first-pass effect in the liver that typically occurs with oral estrogen formulations.[17]

# Progestin Only Methods

## Progestin Oral Contraceptive Pill (POP)

POPs are an alternative option for patients unable to take combination hormone pills who still wish to take an oral medication. The classic POP (norethindrone 0.35 mg) does not reliably suppress ovulation, and must be taken at the same time every day to be effective. This POP works via thickening of cervical mucous as well as altering the endometrial lining. Newer POP formulations (drospirenone 4mg) effectively suppress ovulation and have a flexible 24 hour missed pill window. It can be taken so that a withdrawal bleed occurs monthly or in a continuously, similarly to CHCs.[18]

## Injectable Depot Medroxyprogesterone Acetate (DMPA)

DMPA is a 150 mg/mL intramuscular injection, or 104 mg/0.65 mL subcutaneous injection typically administered every 12 to 15 weeks. Amenorrhea is commonly achieved with repeated doses. DMPA can negatively impact bone health and may not be an optimal choice for those at risk for low bone density.[19]

## Subdermal Implant

The subdermal implant is available in a single rod (etonorgestrel 68 mg) or double rods (levonorgestrel 75 mg) formulation. It is inserted in the inner side of the upper non-dominant arm and can remain there for up to 4 and 5 years, respectively.[20] These methods are long-lasting, reversible, and provide highly effective contraception. While progestin only implants are an extremely effective form of contraception, they can also cause significant unscheduled bleeding at times limiting their tolerability. This method has fewer absolute contraindications to it use and fewer drug–drug interactions compared to other methods.[21,22]

## Intrauterine Devices

Hormonal IUDs work by releasing levonorgestrel locally. There are multiple mechanisms by which this method works including thickening the cervical mucus and thus inhibiting sperm, suppressing ovulation, and thinning out the uterine lining.[23] IUDs have excellent efficacy for contraception and are an option for those that want to avoid systemic absorption of hormones and provide pregnancy prevention up to 3–8 years and have varying amounts of progestin. The 52 mg LNG IUD is an FDA approved treatment for menorrhagia, in addition to providing contraception.

# Emergency Contraception

Women who report recent unprotected intercourse (within 72–120 hours) because of failure of method (eg, torn condom), non-adherence to their contraceptive method (eg, missed pill), or no current use of contraception have the option to use emergency contraception. If there is concern for poor absorption of an oral agent or if BMI is elevated (>35 kg/$m^2$), an IUD should be considered as these situations would reduce efficacy of the oral agents. IUD methods are beneficial because they can continue to provide contraception 3–12 years after placement; they can also be removed after the patient's next menstrual period if ongoing IUD use is not desired. The LNG 52 mg IUD and the copper IUD are equally efficacious for emergency contraception, as demonstrated in a recent randomized noninferiority trial.[24] Methods, dosing, and window of use recommendations are outlined in Table 2. It is important to note that despite recent efficacy data, LNG IUDS are not universally recognized as emergency contraception and there are no formal recommendations in WHO MEC guidelines regarding their use for EC at this time.

**Table 2** Emergency Contraception

| Method | Dose | Efficacy Window |
|---|---|---|
| Oral ulipristal acetate | 30 mg | Within 120 hours |
| Oral levonorgestrel (LNG) | 1.5 mg | Within 72 hours |
| Combined oral estrogen and LNG contraceptive pills | 100 mcg of ethinyl estradiol and 0.5 mg of LNG* | Within 120 hours |
| LNG intrauterine device** | 52 mg | Within 120 hours |
| Copper intrauterine device | 380 $mm^2$ | Within 120 hours*** |

**Notes**: *Repeat dosing in 12 hours is required. **While there is evidence to show LNG IUD an effective form of EC, this method is not universally recognized as EC and not included in WHO guidelines*** can be inserted beyond 5 days after condom less intercourse if not >5 days after ovulation.

# Contraception in Medically Complex Adolescents and Young Adults: Case Studies

To highlight the complexities of contraception prescription in adolescents and young adults (AYA) with medical complexity, we review three cases of adolescents living with chronic medical conditions: HIV, autoimmune disease [ie systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD)], and solid organ transplant (SOT). Given the relative risk of pregnancy, these patients should be counseled on the use of the safest and most reliable contraception methods while considering their chronic medical conditions, clinical severity, and preferences. Institution approval was not required as the cases below were adapted from real clinical scenarios for teaching purposes and contain no identifiable information.

## HIV

### Case

The patient is a 20-year-old female living with HIV who presents for contraception counseling. She was diagnosed with HIV 6 months ago and is currently not taking anti-retroviral (ARV) therapy. She has no other significant past medical history. At her last visit with her infectious disease provider, her labs showed a low viral load and high CD4 count. She is in a new relationship with a male partner (third lifetime sexual partner) and wants to start birth control. She is clinically well appearing in your office. She wants to know what her options for birth control are, but is most interested in the transdermal patch.

### Overview

Women aged 13–24 years accounted for 40% of HIV diagnoses among all women in 2018.[25] The majority (83.6%) of pregnancies among adolescents living with HIV were unintended.[26] Contraception options for women living with HIV have expanded and can decrease the rate of unintended pregnancies, subsequently reducing maternal mortality and perinatal transmission of HIV.[27] Many factors need to be taken into consideration. If the patient is considered not clinically well (CD4 cell count <200 cells/microL defined as acquired immunodeficiency syndrome (AIDS) or the presence of any AIDS-defining illness regardless of the CD4 cell count or not on ARV therapy), their eligibility for certain contraception options will be affected. The impact of contraception on disease progression, viral shedding (which can impact infectivity), and pharmacokinetic interactions also influence contraception choice and management. Lastly, it is important to counsel that non-barrier contraception does not prevent the transmission of HIV or other STIs.

## Current Contraception Recommendations/Methods

### Barrier Methods and Spermicides

Dual protection, meaning concurrent use of an effective hormonal contraception method and condom use, not only reduces the risk of unplanned pregnancy but also lowers the risk of HIV transmission to the partner not living with HIV, and exposure to other STIs including high-risk HPV types. While women with HIV can use condoms without restriction, condoms lubricated with spermicide (and spermicide on its own) are not recommended (Category 3) secondary to the presence of the chemical nonoxynol-9.[28] This ingredient causes vaginal irritation and epithelial erosion that can subsequently increase the risk of HIV acquisition and transmission.[29] Studies have also shown that condoms lubricated with spermicide have a short shelf life and are not more effective in lowering pregnancy risk compared to other lubricated condoms.[30] However, if spermicide-lubricated condoms are the only option, it is better to use this method in lieu of no method at all.

### Estrogen Containing Methods

Women living with HIV are eligible to use estrogen containing methods (Category 1). However, providers must take into consideration common drug-drug interactions between ARV and estrogen containing contraception methods.

## Progestin Only Methods

Women with HIV infection are eligible to use progestin only methods (either Category 1 or 2) depending on the individual's clinical status (eg, viral load, CD4 count) and whether they are on ARV therapy.

## Depot Medroxyprogesterone Acetate (DMPA)

Early studies showed that DMPA may be associated with increased viral replication and decreased immune regulation within the female genital tract, thus potentially increasing risk for HIV transmission.[31,32] However, the Evidence for Contraceptive Options and HIV Outcomes randomized trial showed no significant increase in HIV acquisition risk for women living in an area with a high incidence of HIV using intramuscular DMPA compared to those using the copper IUD or the levonorgestrel (LNG) implant.[33] DMPA can be used without restriction in clinically well HIV positive women (Category 1) and can generally be used (Category 2) in those meeting criteria for not clinically well.

## Intrauterine Devices

IUDs can generally be both initiated and continued in women diagnosed and living with HIV (Category 2 due to concerns for drug–drug interactions discussed more in detail below). However, patients with HIV who are not clinically well and/or not receiving ARV therapy, should not initiate IUD use (Category 3) due to an increased risk of pelvic infection within the 21 days after insertion. IUD complication rates in women living with HIV are comparable to women not living with HIV.[34]

## Drug-Drug Interactions

Anti-retroviral medications (ARVs) have the potential to affect the efficacy of contraceptive methods; contraception methods also have the potential to impact the efficacy of ARVs. These drug–drug interactions can result in increased drug toxicity, unintended pregnancy, and morbidity. Contraceptive failure because of pharmacokinetic interactions of co-medication is a significant concern when counseling about contraception options. Below is a brief overview of interactions that can occur with specific classes of ARVs.

## Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTI's have no significant clinical impact on combined estrogen and progestin, progestin-only options, or barrier contraceptive methods.

## Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Efavirenz (EFV) can reduce ethinyl estradiol and progestin concentrations in women taking oral contraception.[35,36] The combination of EFV and combined hormonal contraception methods is classified as Category 2. Serum levels of the progestin components of hormonal contraception pills (norgestimate and levonorgestrel) and the levonorgestrel implant were reduced when used in conjunction with EFV. Women using levonorgestrel implants had increased pregnancy rates (ie, rates of contraceptive failure) when taking EFV-containing ARV therapy compared with women with an implant but no ARV use.[37,38] The effect of EFV on levonorgestrel also needs to be taken into consideration when prescribing emergency contraception; emergency contraceptive options that contain levonorgestrel as the active ingredient can generally be used but close follow-up is recommended (Category 2). As a result of these common interactions, it is important to reinforce the importance of using barrier methods in conjunction with hormonal methods for individuals taking efavirenz.[35]

## Protease Inhibitors (PIs)

Protease inhibitors can be separated into two major classes: ritonavir-boosted and protease inhibitors without ritonavir. PIs without ritonavir increase levels of both ethinyl estradiol and progestin in those taking combined hormonal contraception methods (Category 2). These increases can lead to adverse effects such as headache, fatigue, and nausea.[39,40] For those patients specifically taking fosamprenavir, combined hormonal contraceptives are generally avoided (Category 3);

CHCs can decrease levels of fosamprenavir therefore decreasing the efficacy of non-ritonavir boosted PI. Conversely, ritonavir-boosted PIs have the potential to reduce the effectiveness of combined hormonal contraceptives (Category 2) by decreasing ethinyl estradiol and increasing progestin concentrations.[41,42]

If primary care providers who care for AYA living with HIV do not have experience prescribing and managing ARVs, they should consult with an infectious disease specialist to discuss drug-drug interactions in more detail. ARVs continue to evolve and all drug interactions as outlined by the World Health Organization can be reviewed at (https://www.who.int/news/item/29-08-2019-new-app-for-who-s-medical-eligibility-criteria-for-contraceptive-use)

## Case Conclusion

This patient is clinically well based upon her lab work and physical examination. Since she is not on ARV therapy currently, there is no concern for drug–drug interactions. She is interested in the transdermal patch that is changed weekly. She agrees to STI screening, and she has already completed the HPV vaccine series. Cervical cancer screening is recommended within 1 year of sexual debut and no later than age 21 years for individuals diagnosed with HIV before age 21 years old.[43] Therefore, a pap smear should be discussed at this visit. She is 70kg, and does not have any contraindications to estrogen. If she decides to begin ARV therapy in the future, drug–drug interactions will have to be reviewed. It was recommended that she use condoms at every sexual encounter to prevent transmission of HIV and other STIs.

# Autoimmune Disease

## Case

Patient is a 17-year-old with Crohn disease. She experiences monthly menstrual cycles, often associated with nausea, pain, and cramping that keep her home from school. Her bleeding is described as "heavy", and she occasionally has menstrual accidents. Her inflammatory bowel disease (IBD) is currently in remission; she has been on a stable dose of adalimumab for one year. She has had two previous bone fractures (wrist and clavicle); one occurred after a skateboarding accident and the other after a fall on the soccer field. She is interested in options for controlling her bleeding and pain. On confidential questioning, she is interested in both males and females; she has never been sexually active although thinks this may change once she leaves for college next year and would like to pro-actively discuss contraceptive methods.

## Overview

Autoimmune disorders are commonly present during adolescence, and occur more frequently in women. These diverse conditions (including IBD, rheumatoid arthritis, systemic lupus erythematosus) share a common pathway of inflammation and immune dysfunction.[44] Many of the medications utilized to treat or control these disorders act by suppressing the immune system.[45]

Often, disease incidence peaks during the reproductive years, a time when many patients benefit from menstrual management or contraception. Despite this need, many women with autoimmune disorders do not use any contraceptive method.[46] If a method is used, it is less likely to be a highly effective method. Gawron et al[44] demonstrated that 23% of women of childbearing age with IBD did not use any contraception, and only 17% utilized an IUD.

Many factors, such as route of administration and ease of use, should be considered in decision making for patients with autoimmune conditions. Patients with active medical illnesses may have frequent medical appointments or multiple medications to take daily. These can pose challenges with adherence. The patient's risk for thrombosis or for low bone density for age must be assessed.

Even if contraception is not needed, medications or devices commonly used for birth control may be important options for menstrual management. Women with gastrointestinal (GI) diseases may not be able to utilize NSAIDs, limiting treatment options for dysmenorrhea. Women with IBD commonly experience worsening GI symptoms during the menstrual cycle, including increases in nausea (30% vs 7%), flatulence (53% vs 22%), and abdominal pain (68% vs 38%), compared to healthy controls.[47] The exacerbation of symptoms may be due to endometrial prostaglandins leading

to increased inflammation and GI motility. Cyclic GI symptoms improve with use of either combined hormonal contraceptives or a hormonal IUD. With exogenous hormone (CHC) use, GI symptoms did not worsen.[48]

# Current Contraception Recommendations

## Estrogen Containing Methods

Some studies have suggested an association between use of oral contraceptive pills and risk of IBD. In the Nurses' Health Study, the hazard ratio for developing Crohn disease was 2.82 in current CHC users and 1.39 in past users (compared to never users), controlled for smoking and other confounders.[49] In a meta-analysis of 20 studies, the risk of developing IBD was 30% increased in women exposed to CHCs compared to those who never took this medication.[50] However, these population-level studies are subject to many biases, including the indication for CHC use, recall bias, and the rarity of IBD diagnosis. CHC use has not been consistently implicated in the development of rheumatologic disorders; in some cases, it appears to even have a potential protective effect.[45]

True data regarding the safety of the various contraceptive options for women with autoimmune conditions are lacking. Many of the recommendations are based upon consensus rather than evidence. The biggest concern regarding use of estrogen containing medications in the setting of autoimmune disease is the risk of VTE. If a patient with SLE is known to have no antiphospholipid antibodies or thrombocytopenia, all hormonal and non-hormonal contraceptives are considered safe (Category 1 or 2). In contrast, all estrogen-containing methods are contraindicated if someone with SLE has positive or unknown anti-phospholipid antibodies because of increased thrombosis risk (Category 4).

Similarly, the risk of VTE is increased 3 to 8-fold in women with active IBD. VTE risk is also increased in patients with IBD who have had recent surgery, immobilization, dehydration, or who are taking chronic corticosteroids. Use of estrogen-containing medications additionally increases the risk of VTE 2-fold over baseline. These additive risks for this serious outcome likely outweigh the benefits of estrogen-containing medications. The WHO has indicated that use of CHCs in this setting is a Category 3. Thus, disease activity influences decisions. Currently, we do not have information on the effect of recently marketed "natural" estrogens (estradiol valerate, estetrol) on autoimmune diseases to make any specific recommendations regarding these newer medications.

In patients with malabsorption, CHCs are a Category 2, due to concerns about insufficient GI absorption of the medication and the potential for diminished efficacy. There is no evidence that CHCs cause disease progression or relapse for IBD, SLE, or rheumatoid arthritis.[51] In a multi-center study of women with SLE, participants were randomly assigned to CHCs, progestin only contraceptives, or a copper IUD. Disease activity remained mild and stable in all groups throughout the trial, leading to the conclusion that hormonal therapy did not influence disease course.[52]

## Contraceptive Patch and Transvaginal Ring

The transvaginal and transdermal routes of administration avoid the liver "first pass" effect of estradiol. This mode of administration may be optimal for patients with (or at risk for) liver disease related to autoimmune causes, IBD, or concurrent medication use.

## Progestin Only Methods

Progestin only contraceptives are currently thought to be safe in patients with SLE and positive antiphospholipid antibodies as progestins do not have the same pro-thrombotic effect. However, some groups advocate for avoidance of hormone-containing contraception altogether and suggest the copper IUD or barrier methods. No association between use of progestin only contraception and risk of autoimmune disease has been consistently demonstrated.[53]

## Progestin Only Pills

The failure rate for POPs may be higher in patients with malabsorption. Norethindrone acetate is a good oral option for menstrual management. However, it is not FDA approved as a contraceptive. Doses higher than 10 mg daily are not recommended, as they appear to be associated with formation of hepatic adenomas, maybe in part due to its in vivo conversion to estradiol.[54]

### DMPA

In patients with SLE and thrombocytopenia, DMPA is a Category 3, due to the risk of increased uterine bleeding. Given the known deleterious impact of DMPA on the skeleton, DMPA may not be the optimal choice for patients with additional risk factors for low bone density (eg, IBD, steroid use, malnutrition, lack of weight bearing activity, vitamin D deficiency).[55]

### Subdermal Implant and Intrauterine Devices

The bleeding profile may be persistently irregular with these methods, and patients should receive appropriate education regarding this potential outcome. Treatment of heavy menstrual bleeding may be important for patients with IBD who can suffer from anemia, and patients with SLE complicated by thrombocytopenia. No increased rates of infection with the IUD have been reported.[51]

### Case Conclusion

In addition to wanting an effective method of birth control, our patient desired control of menses due to pain, nausea, and heavy bleeding. After shared decision making, she opted to begin use of the contraceptive ring. She wanted a method that did not require daily administration, and one that would provide predictable menstrual bleeding rather than irregular cycles. Her disease was in remission, making choice of an estrogen-containing medication appropriate at this time.

## Solid Organ Transplant

### Case

Patient is a 17-year-old female with a history of end stage renal disease status post a living related donor transplant at age 15. She is currently on dual immunosuppressant therapy which she has taken for the last year without interruption. At the visit today, she is noted to have a stable blood pressure reading (122/78 mm Hg). Her most recent labs drawn in past month show an in-range sirolimus level and stable allograft creatinine level (1.14 mg/dL). On confidential history today, she has recently become sexually active (penile-vaginal sex) with her male partner and reports 100% condom use.

### Overview

The number of solid organ transplants has nearly tripled over the past 30 years.[56] Pediatric and adolescent transplants are much a smaller piece of total transplants, with 80% of recipients across the major solid organ transplants (kidney, liver, heart, lung, intestine) surviving into young adulthood. Improved survival rates increase the likelihood that primary care providers will be caring for young women post-transplant who desire contraception.

Studies show that more than half of AYA renal transplant recipients (ages 13–23 years) are sexually active, a rate comparable to the general AYA population. Despite these behaviors, contraception use is poor.[57,58] Studies of kidney and liver transplant patients have shown that up to half of women are not using contraception consistently after transplantation, and more than a third of conceptions in women who did conceive post-transplant were unplanned pregnancies.[59,60] Multiple studies among both adolescent and adult solid organ transplant recipients demonstrate low rates of receipt of sexual health counseling from their providers.[61–63]

Adolescents have the highest rates of rejection related graft loss of any age group.[64–70] Unplanned pregnancy in this group can further exacerbate negative health outcomes. The CDC currently lists solid organ transplant within the last two years as a condition that can lead to adverse events as a result of pregnancy with potential negative impact on graft function. Rose et al found that women who became pregnant within 2 years after kidney transplantation were at increased risk of graft failure compared to pregnancies more than 2 years after transplant.[71] Additionally, many of the medications used post-transplant including immunosuppressive medications are considered teratogenic and may negatively impact the fetus. Mycophenolate mofetil (MMF), a commonly used agent in conjunction with calcineurin inhibitors, is associated with higher risk of spontaneous abortion and may result in structural malformations in the offspring including cleft palate, esophageal, cardiac, and kidney abnormalities.[72,73] Other immunosuppressant medications including azathioprine

and glucocorticoids have been associated with increased risk of fetal growth restriction, prematurity, and low birth weight.[74–76]

When counseling AYA on contraceptive methods, providers should be aware that solid organ transplants are divided into two categories. Complicated transplants include those with graft failure (either acute or chronic), rejection, or transplant vasculopathy. Estradiol is contraindicated in these cases due to increased risk for thrombosis. For women with uncomplicated transplants, all forms of contraception are allowed (in the absence of other co-morbidities) including combined estrogen-progestin methods.

## Current Contraceptive Recommendations/Methods

### Barrier Methods

Professional transplant societies recommend barrier methods with an additional form of contraception for all transplant patients at risk for pregnancy until pregnancy is desired and careful planning occurs between transplant and obstetrics teams.

### Estrogen Containing Methods

Combined estrogen and progestin methods are considered safe in uncomplicated transplants (category 2), but contra-indicated in complicated transplants (Category 4). CHCs are also to be avoided in cases of decompensated cirrhotic liver disease, hypertension, and abnormal renal function which can be common co-morbidities in this population. Patients should be seen back for follow-up several months after starting on a CHC method to monitor blood pressure and to assess proper use efficacy.

### Progestin-Only Methods

Progestin-only options can generally be used for patients with both complicated and uncomplicated transplants as these methods are not associated with increased risk of thrombosis or hypertension.

### DMPA

Transplant recipients are at a four-fold higher risk of fracture compared with the general population secondary to high-dose or prolonged glucocorticoid therapy during the initial phase of immunosuppression for recurrent episodes of rejection.[77] DMPA, which can negatively impact bone health may not be an optimal choice.[77] DMPA is also associated with weight gain which can also be an issue with glucocorticoid use.

### Subdermal Implant

Lew et al found that among reproductive age women who had received a solid organ transplant, implant users had no increased transplant-related complications or infections compared to age and organ-match controls.[78] Additionally, no solid organ transplant recipients had unplanned pregnancies while using the implant.[78]

### Intrauterine Devices

Uncomplicated transplants are considered Category 2 for both initiation and continuation of all IUD types. However, for complicated transplant patients, IUD initiation is generally not recommended (Category 3) as these patients are often on higher doses of immunosuppressant medication with potential increased infection risk. If an IUD has already been placed, it is not considered to add any additional risk.

Of note, historically IUDs were strongly discouraged in women who had received transplants secondary to a 1981 case report that documented failure of the Cu-IUD in two renal transplant patients. The American Society of Transplantation (AST) had issued a consensus statement in 2005 recommending against IUD use citing concerns that immunosuppressant regimens would impair the sterile inflammatory reaction within the uterus, thus rendering the IUD ineffective and increasing the potential risk of pelvic infections. However, over the last several decades, there has been a lack of evidence to support these concerns. Subsequent observational studies and case series report no unintended

pregnancies in transplant recipients using either the copper or LNG IUD, and have demonstrated overall IUD effectiveness.[79,80]

## Case Conclusion

Our patient's recent transplant and subsequent course are categorized as uncomplicated. She was counseled on contraception options and ultimately chose to start combined hormonal contraceptive pills. She was counseled on continuing condom use for STI prevention and also had Pap testing per guidelines recommending initiation of screening at time of coitarche if under age 21 and immunocompromised. She had previously completed HPV vaccinations prior to transplant.

# Conclusion

Contraception plays a significant role in the reproductive health care of AYA, especially in those with medical complexity for whom an unplanned pregnancy could pose additional health risk. Although AYA with chronic illnesses often interface more frequently with the health care system than healthy AYA, they may see their specialists more than their primary care providers. Sensitive conversations, such as those soliciting a sexual history and assessing contraceptive need, are sometimes overlooked in the setting of other medical needs. However, comprehensive sexual and reproductive health care of these patients is critical to optimize health. There are multiple factors that must be taken into consideration by providers when thinking about contraceptive counseling including clinical status, co-morbidities, risk for thrombosis, drug–drug interactions, safety, and effectiveness. Health care providers should follow evidence-based guidelines (MEC for contraceptive use) in their home region when in engaging in contraceptive counseling.

# Ethics Statement

Institutional approval was not required to publish the case details as they were adapted from real cases.

# Author Contributions

Dr. Addison drafted the initial manuscript, substantially revised and critically reviewed the manuscript and approved the final manuscript as submitted. Dr. Hassan and Dr. DiVasta substantially revised or critically reviewed the article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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# Disclosure

Jessica Addison and Areej Hassan are co-first authors for this study. Dr Areej Hassan is a nexplanon trainer for FDA mandated device training with health care providers. Dr Amy DiVasta is an investigator for the initiated research for a QI project with grant received from Organon. All authors report no other potential conflicts of interest for this work.

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