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WOMEN'S HEALTH CARE PHYSICIANS

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The North American Society for Pediatric and Adolescent Gynecology endorses this document. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care in collaboration with committee members Meredith Loveless, MD and Kimberly Hoover, MD.

Genetic Syndromes and Gynecologic Implications in Adolescents

ABSTRACT: As adolescents with a genetic syndrome transition to adult medical care, they may be referred to obstetrician–gynecologists for routine preventive or contraceptive services, screening, or counseling for sexually transmitted infection, or for menstrual management. Although some genetic syndromes have no physical or intellectual impairment, others have significant ones; therefore, education and gynecologic care should be based on a patient's intellectual and physical capabilities. It is important to remember that adolescents with or without a genetic syndrome are sexual beings. Thus, education about reproductive health, expectations for fertility, and healthy relationships is important when treating patients with genetic syndromes. Obstetrician–gynecologists must respect patient autonomy and avoid coercion in any discussions with a patient, including decisions about contraceptive choices, sexual activity, and pregnancy planning. Most patients who have genetic syndromes and are neurotypical can tolerate routine gynecologic examinations in the office, when necessary. A patient should not be forced to have an examination or be restrained for an examination. Obstetric care of adolescents and women with genetic syndromes can pose challenges and often requires a multidisciplinary approach from the time pregnancy is contemplated through the postpartum period. When caring for an adolescent with a genetic syndrome, individual patient and guardian concerns, medical diagnoses associated with the specific genetic syndromes, and medication interactions should be considered. Obstetrician–gynecologists are encouraged to seek out additional resources and expertise when caring for adolescents with underlying genetic syndromes.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists offers the following recommendations and conclusions:

- Obstetrician–gynecologists are encouraged to seek out additional resources and expertise when caring for adolescents with underlying genetic syndromes.
- Although some genetic syndromes have no physical or intellectual impairment, others have significant ones; therefore, education and gynecologic care should be based on a patient's intellectual and physical capabilities.
- Obstetrician–gynecologists must respect patient autonomy and avoid coercion in any discussions with a patient, including decisions about contraceptive choices, sexual activity, and pregnancy planning.
- Patients with an underlying genetic syndrome should be offered age-appropriate gynecologic screening and human papillomavirus vaccination.
- When an examination is necessary but not urgent for a patient who cannot tolerate in-office examination, the obstetrician–gynecologist should attempt to coordinate the examination with other procedures that require sedation, such as dental work.
- Obstetrician–gynecologists should be aware of any unique surgical or anesthesia risk associated with the adolescent's genetic syndrome.

Many genetic syndromes have unique implications for reproductive health care. As adolescents with a genetic syndrome transition to adult medical care, they may be referred to obstetrician–gynecologists for routine preventive or contraceptive services, screening, or counseling for sexually transmitted infection (STI), or for menstrual management. This Committee Opinion highlights common reproductive health considerations, and Table 1 lists important gynecologic, contraceptive, and reproductive considerations for patients with genetic syndromes that may present to an obstetrician–gynecologist. Obstetrician–gynecologists are encouraged to seek out additional resources and expertise when caring for adolescents with underlying genetic syndromes. For information on specific genetic syndromes, the obstetrician–gynecologist may seek subspecialty referral or online information from sources such as the National Institutes of Health's National Center for Advancing Translational Sciences and National Human Genome Research Institute (1). In some regions, telemedicine options with subspecialists are emerging.

Preventive gynecologic health care needs for patients with a genetic syndrome are similar to those of their peers without a genetic syndrome. Although some genetic syndromes have no physical or intellectual impairment, others have significant ones; therefore, education and gynecologic care should be based on a patient's intellectual and physical capabilities (2). It is important to remember that adolescents with or without a genetic syndrome are sexual beings. Thus, education about reproductive health, expectations for fertility, and healthy relationships is important when treating patients with genetic syndromes (3, 4). Obstetrician–gynecologists should be aware that patients with a physical or developmental disability, or both, are at higher risk of sexual assault compared with their peers without special needs and should screen them, as with all patients, for a history of sexual assault (5). Screening for STIs in this population should be considered. When treating adolescents who have experienced sexual violence, obstetrician–gynecologists should be familiar with laws and regulations that may require reporting to law enforcement authorities.

For those obstetrician–gynecologists and other health care providers who care for medically complex adolescent patients, the importance of contraception to prevent unintended pregnancy should be stressed. Obstetrician–gynecologists may reference the Centers for Disease Control and Prevention's *U.S. Medical Eligibility Criteria for Contraceptive Use* (6). Expert consultation should be requested if questions remain regarding the safest choices for contraception.

Gynecologic Evaluation of Females with Genetic Syndromes

As with all adolescent patients, the decision to perform an examination should be based on indication. If the patient can participate in conversation, a confidential interview to discuss sexual activity and sexuality is recommended. Obstetrician–gynecologists must respect patient autonomy and avoid coercion in any discussions with a patient, including decisions about contraceptive choices, sexual activity, and pregnancy planning. Before the examination of a patient, it is important to assess her quality of life and functional physical skills. History taking may include toileting and the ability to maintain menstrual hygiene when at school or work; this information is important when helping the patient achieve her goals for activities of daily living. Patients with an underlying genetic syndrome should be offered age-appropriate gynecologic screening and human papillomavirus vaccination (7). Most patients who have genetic syndromes and are neurotypical can tolerate routine gynecologic examinations in the office, when necessary. A patient should not be forced to have an examination or be restrained for an examination. Referral to a gynecologic care provider with experience and expertise in this population can be made, if needed. A pelvic examination should be performed, when necessary, for gynecologic care, such as for the evaluation of vaginal discharge or pelvic pain, or for STI testing, if indicated. Urine also may be collected for STI screening.

When an examination is necessary but not urgent (eg, cervical cancer screening or placement of an intrauterine device [IUD]) for a patient who cannot tolerate in-office examination, the obstetrician–gynecologist should attempt to coordinate the examination with other procedures that require sedation, such as dental work. If sedation or anesthesia services are needed, an anesthesia consultation before the procedure may be beneficial in this population. Obstetrician–gynecologists should be aware of any unique surgical or anesthesia risk associated with the adolescent's genetic syndrome. This could include need for careful placement and transfer of the patients to and from the procedure table to minimize cervical spine strain, fracture, or hypermobility-related injury associated with syndromes such as skeletal dysplasia and connective tissue disorders.

Obstetric Considerations

Obstetric care of adolescents and women with genetic syndromes can pose challenges and often requires a multidisciplinary approach from the time pregnancy is contemplated through the postpartum period. These patients should have a preimplantation genetic counseling evaluation with their obstetrician–gynecologists, medical geneticists, maternal–fetal medicine specialists, or other appropriate subspecialists to optimize care. Some of these syndromes can have a substantial effect on the health of a woman, her fetus, or both, during pregnancy, and the patient should be counseled about those risks before pregnancy.

Table 1. Genetic Syndromes and Gynecologic Implications

Syndrome (Mode of Inheritance)	Key Features for the Gynecologist
Angelman syndrome (Most cases de novo)	Developmental delay: Yes • Seizure disorder • Menstrual hygiene or management
CHARGE (Coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) syndrome (Autosomal dominant; most of which are caused by de novo mutations)	Developmental delay: Possible • Obsessive compulsive disorder • Delayed puberty • Menstrual hygiene or management • High risk of anesthesia complications; anesthesia consultation recommended. • Structural and functional heart disease may limit contraceptive options.
Cystic fibrosis (Autosomal recessive)	Developmental delay: No • Delayed puberty • Abnormal uterine bleeding • Multifollicular ovaries or PCOS • Increased risk of osteoporosis • Risk of gallbladder disease • Urinary incontinence • Risk of HPV-associated dysplasia when transplanted and immunosuppressed • Recurrent vaginal candidiasis
DiGeorge syndrome (22q11.2 deletion syndrome) (Usually de novo; 10% of cases are inherited in an autosomal dominant manner)	Developmental delay: Possible; learning differences, behavioral issues on the autism spectrum • Menstrual hygiene or management • Structural and functional heart disease may limit contraceptive options • Immune system deficiencies • Thyroid dysfunction • Hypocalcemia • Growth hormone deficiency
Down syndrome (95% de novo; 4% result of a parent with a balanced translocation)	Developmental delay: Variable • Ovulatory dysfunction leading to AUB • PMS • Dysmenorrhea • Menstrual hygiene or management • Atlantoaxial instability can cause spinal cord injury when positioning for anesthesia • Structural and functional heart disease may limit contraceptive options • Obesity

(*continued*)

Table 1. Genetic Syndromes and Gynecologic Implications (*continued*)

Syndrome (Mode of Inheritance)	Key Features for the Gynecologist
Ehlers-Danlos—hypermobile type (most common, least severe of subtypes) (Autosomal dominant, inheritance pattern varies by type)	Developmental delay: No • Dysmenorrhea • Pelvic organ prolapse • Urinary incontinence • Diastasis of pubic symphysis causing dyspareunia • Care positioning of patient associated with mobility issues (hypermobility)
Ehlers-Danlos—vascular type (rarest, most severe subtype) (Autosomal dominant)	Developmental delay: No • AUB • Endometriosis • High operative risk due to vascular fragility, failure to control bleeding, wound dehiscence, failure of suture to hold tissue • LARC methods might be the best choice for females with conditions that are associated with increased risk of adverse health events as a result of pregnancy • Concern for potential increased risk of uterine perforation
Epidermolysis bullosa (Four subtypes; most are autosomal dominant; rarely autosomal recessive)	Developmental delay: No • Delayed puberty • Labial and vaginal adhesions; avoid tampons, applicators for medication, vaginal penetration • Avoid internal vaginal examinations for screening • Skin or mucous membrane trauma depending on severity of disease (eg, avoid skin adhesive, intravaginal ring, injections, LARC methods) • Increased risk of UTI due to urethral stricturing • Urinary retention
Fanconi anemia (Inherited most commonly in an autosomal recessive pattern; rarely X-linked recessive pattern)	Developmental delay: Variable • Pancytopenia • AUB • Growth hormone deficiency • Subfertility • Associated with differences in sex development and müllerian anomalies • Primary ovarian insufficiency • Osteopenia • Increased risk of solid tumors, including squamous cell carcinoma of vulva, vagina, cervix; consider HPV screening at age 18 years and biopsy of any genital lesion in vulvar or perianal region • Increased risk of breast cancer; recommendations for screening are similar to those patients at high risk of cancer due to *BRCA* mutations, including use of mammography and MRI
FMR1-related disorders (Fragile X syndrome) (X-linked, triplet repeat disorder)	Developmental delay: Variable; autism spectrum • Seizure disorder • Ovarian insufficiency (associated with premutation carrier) • Subfertility • Precocious puberty in females with *FMR1* full mutation

(*continued*)

Table 1. Genetic Syndromes and Gynecologic Implications (*continued*)

Syndrome (Mode of Inheritance)	Key Features for the Gynecologist
Marfan syndrome (Autosomal dominant)	Developmental delay: No • Structural and functional heart disease may limit contraceptive options and have pregnancy implications • Cardiovascular standing (eg, valve issues) • LARC methods might be the best choice for females with conditions that are associated with increased risk of adverse health events as a result of pregnancy
McCune-Albright syndrome (Not inherited)	Developmental delay: No • Bone, skin, and endocrine disorder associated with peripheral precocious puberty; menarche as early as age 2 years; this may or may not be preceded with thelarche and adrenarche • Ovarian enlargement mistaken for ovarian tumor can lead to unnecessary oophorectomy • Heavy menstrual bleeding • Careful positioning of patient because of potential increased risk of fracture
Neurofibromatosis type 1 (Autosomal dominant)	Developmental delay: Variable; some learning disability • Attention-deficit/hyperactivity disorder • Delayed puberty or precocious puberty • Cardiovascular involvement (eg, coarctation or pulmonary hypertension) • Increased risk of breast cancer; consider breast cancer screening starting at age 30 years
Noonan syndrome (Autosomal dominant)	Developmental delay: Usually normal but can show some mild intellectual disability • Urogenital anomalies • Delayed puberty • Potential for heavy menstrual bleeding due to blood clotting defects and platelet dysfunction • Structural and functional heart disease may limit contraceptive options
Peutz-Jeghers syndrome (Autosomal dominant and de novo)	Developmental delay: No • AUB • Precocious puberty • Increased risk of colon cancer, cervical cancer, endometrial cancer, uterine cancer, and ovarian cancer, including sex cord stromal tumors; ovarian sex cord tumors with annular tubules, borderline ovarian tumors • An 18% lifetime risk of gynecologic malignancy; prompt evaluation for AUB needed because of the risk of endometrial cancer • Screening for gynecologic malignancy includes ovarian tumors, consider yearly pelvic ultrasonography • Breast cancer, clinical examination every 6 months starting at age 25 years • Cervical cancer (risk of adenoma malignum); screen annually beginning at age 18–20 years

(*continued*)

Table 1. Genetic Syndromes and Gynecologic Implications (*continued*)

Syndrome (Mode of Inheritance)	Key Features for the Gynecologist
Prader–Willi syndrome (Multiple molecular mechanisms, most de novo)	Developmental delay: May have intellectual disabilities • Short stature due to growth hormone deficiency • Delayed puberty • Hypogonadotropic hypogonadism • Primary amenorrhea • Osteopenia or osteoporosis • Obesity due to binge eating • Obsessive compulsive tendencies
Sickle cell disease (Autosomal recessive)	Developmental delay: No • Delayed puberty • Hypothalamic amenorrhea • Osteopenia • All contraception options are generally safe; progestin-only contraception may assist in decreasing painful episodes, but copper IUD may increase bleeding • Increased risk of deep vein thrombosis
Sotos syndrome (More than 95% de novo)	Developmental delay: Yes • Menstrual hygiene or management • Ovarian fibromas • Seizure disorder
Sturge–Weber syndrome (Not inherited)	Developmental delay: Variable • Menstrual hygiene or management • Seizure disorder • Hypothyroid • Growth hormone deficiency
Tuberous sclerosis complex (Autosomal dominant or de novo)	Developmental delay: Variable • Menstrual irregularity • Primary ovarian insufficiency • PCOS • No restriction on contraceptive method type in absence of hypertension with normal renal function; use caution with combined oral contraceptives because of lymphangioleiomyomatosis
Turner syndrome (Most cases are not inherited)	Developmental delay: Variable • Delayed puberty • Primary amenorrhea • Monitor for symptoms of ovarian insufficiency • Gonadal dysgenesis with possible mosaicism • Risk of gonadoblastoma (when Y chromosome or chromatin is present) • Risk of low bone density (consider obtaining a baseline DXA) • Growth hormone insufficiency • LARC contraceptive methods might be the best choice for females with conditions that are associated with increased risk of adverse health events as a result of pregnancy • High risk of aortic dissection during pregnancy • Lichen sclerosus

(*continued*)

Table 1. Genetic Syndromes and Gynecologic Implications (*continued*)

Syndrome (Mode of Inheritance)	Key Features for the Gynecologist
VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb) syndrome (Sporadic)	Developmental delay: No • Uterine and vaginal anomalies • Associated with renal abnormalities • Consider structural abnormalities of heart and kidneys when deciding on contraceptive method • Spinal anomalies, consider anesthesia consultation before surgery
Von Hippel–Lindau syndrome (Autosomal dominant, de novo)	Developmental delay: No • Risk of cyst formation in genital tract • Hemangioblastomas • Kidney cysts and renal carcinoma • Pancreatic neuroendocrine tumors • Pheochromocytomas • Endolymphatic sac tumors • Relative contraindication for estrogen-containing medications; effect of progesterone unclear • Copper IUD may be an appropriate contraceptive method
WAGR (Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability) syndrome (Most cases de novo)	Developmental delay: Variable • Gonadal dysgenesis • Ambiguous genitalia • Müllerian anomalies • Increased risk of ovarian cancer (gonadoblastoma) • Lack of specific guidelines for ovarian cancer surveillance, may consider pelvic ultrasonography and CA125 measurement
Williams syndrome (Most cases de novo, transmitted in autosomal dominant manner)	Developmental delay: Variable • Precocious puberty • Avoid vitamin D supplements • Consider cardiovascular and renal involvement when deciding on contraceptive method

Abbreviations: AUB, abnormal uterine bleeding; DXA, dual-energy X-ray absorptiometry; HPV, human papillomavirus; IUD, intrauterine device; LARC, long-acting reversible contraception; MRI, magnetic resonance imaging; PCOS, polycystic ovary syndrome; PMS, premenstrual syndrome; UTI, urinary tract infection.

Cardiac Considerations

When genetic syndromes are associated with structural and functional cardiac disease, the obstetrician–gynecologist should work with the patient's cardiologist and reach consensus before medications are started or procedures performed in at-risk patients. In many cases, methods for contraception and menstrual regulation or manipulation are dependent on the cardiac abnormality and current cardiovascular state. Helpful resources to provide gynecologic care for this population include the American College of Chest Physicians' *CHEST Guidelines and Consensus* (8) and the *U.S. Medical Eligibility Criteria for Contraceptive Use* (6). Gynecologic-specific concerns include the possibility of vagal reaction with IUD insertion; thus, those patients with complex cardiac defects may need cardiac monitoring during placement to observe for arrhythmia. Estrogen-containing medications are contraindicated for many patients with cardiac considerations and should be avoided in patients with an increased risk of thrombosis. Systemic progestin-only contraceptives are considered safe for most patients with congenital heart disease; however, they should be used with caution in patients with congestive heart failure because of the potential for further fluid retention, which may result in cardiac strain (9).

Menstrual Manipulation

A gynecologist may be consulted for menstrual manipulation for adolescents and young women with genetic syndromes. In some individuals with genetic syndromes, a seizure disorder is present; in these cases, menstrual suppression may be used to manage the exacerbation of seizure activity caused by hormonal changes. Interactions between seizure medications and hormonal contraception are common. These interactions have the potential to alter efficacy of anticonvulsants as well as hormonal

contraception. Once the patient or caretaker's underlying goal for gynecologic care is established, the gynecologist should work with the patient's neurologist and reach consensus before starting medications for menstrual management. Notably, depot medroxyprogesterone acetate may be associated with a reduction in seizure activity (10). The *U.S. Medical Eligibility Criteria for Contraceptive Use* also can provide guidance on drug interactions with seizure disorders (6).

In genetic syndromes for which developmental delay is present, caregivers often seek out menstrual suppression to improve menstrual hygiene, for pregnancy prevention, or to reduce exacerbations in behavioral issues that follow a hormonal pattern. For information and guidance on options for menstrual management for adolescents with physical and cognitive disabilities, see Committee Opinion No. 668, *Menstrual Manipulation for Adolescents With Physical and Developmental Disabilities* (2).

Conclusion

When caring for an adolescent with a genetic syndrome, individual patient and guardian concerns, medical diagnoses associated with the specific genetic syndromes, and medication interactions should be considered. As more data become available on genes and inheritance patterns, surveillance and treatment recommendations for patients with genetic syndromes may evolve. Because of the current limitations of literature and data on managing gynecologic issues in individuals with a genetic syndrome, recommendations for screening and intervention largely are based on expert opinion. Table 1 is a guide and does not replace collaboration with the patient's other health care providers or consultation with a health care provider who has expertise in specific genetic syndromes.

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