REPRODUCTIVE HEALTH AND ITS IMPACT ON LIPID MANAGEMENT IN ADOLESCENT AND YOUNG ADULT FEMALES

Ann Liebeskind, MD, Mobile Health Team Lipids Clinic, Neenah and Wauwatosa, Wisconsin, drann@mhtwi.com
Jennifer Thompson, MD, Division of Maternal Fetal Medicine, Vanderbilt University Medical Center, Nashville, TN, jennifer.l.thompson.1@vumc.org
Don Wilson, MD, Department of Pediatric Endocrinology, Cook Children's Medical Center, Fort Worth Texas, don.wilson@cookchildrens.org

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ABSTRACT

Lipids disorders are common in youth. Adolescents and young women of childbearing age who have moderate to severe lipid disorders may benefit from treatment with lipid lowering medications (LLM). However, most of these medications are contraindicated in pregnancy. Those who are sexually active should receive counseling on effective methods to prevent unplanned pregnancies. While contraceptives, when appropriate, are typically prescribed by primary care physicians, lipidologists are often asked to address the unique aspects related to use of long-term LLMs, such as statins, in females with hypercholesterolemia. Appropriate counseling and management require not only knowledge of the effects of sexual maturation on lipid and lipoprotein metabolism, but a thorough understanding of current recommendations and potential harms associated with the use of some LLMs, such as statins, should pregnancy occur. In this chapter, we review changes in lipid and lipoprotein metabolism during puberty, current guidelines for use of contraceptive methods in adolescent and young adult females and laws that pertain to this unique population.

CANDIDATES FOR LIPID LOWERING MEDICATIONS IN YOUTH

There are a number of lipid disorders, both acquired and genetic, that may warrant pharmacotherapy, beginning at an early age. These include primary hypercholesterolemia, such as familial hypercholesterolemia (FH), and the severe hypertriglyceridemia characteristic of familial chylomicronemia syndrome (FCS). A discussion of the specific disorders causing moderate to severe dyslipidemia in adolescents and young adults can be found in Endotext (1-3).

LIPID AND LIPOPROTEIN METABOLISM DURING PUBERTY

It should be noted that lipid levels vary throughout childhood and adolescence. Prior studies have described these changes. At young ages, lipid levels are similar between boys and girls (3-12). Cholesterol levels at birth are typically very low. A review of studies of serum cholesterol in the U.S. concluded that total cholesterol (TC) concentration, which is approximately 65 mg/dl (1.68 mmol/l) in umbilical cord blood, rises after birth to reach a mean level of 165 mg/dl (4.27 mmol/l) by 2 years-of-age (13). When trends are analyzed by chronological age, mean TC levels generally peak between ages 9 to 11, followed

by a decline during puberty. There are gender differences in the levels of other lipids and lipoproteins as well. A review of data from NHANES demonstrated that the prevalence of elevated levels of non-high-density lipoprotein cholesterol (non-HDL-C) was greater in girls (9.4%) than in boys (7.5%) (14). Levels rise again after puberty to reach the adult values.

Since puberty has such a remarkable effect on lipid levels, it is important to understand the stages of pubertal development in assessing and making recommendations for treatment of dyslipidemia in youth. Puberty is defined as the age at or period during which the body of a girl or boy matures and becomes capable of reproduction. Classically, there are five well-defined stages of puberty, often referred to as Tanner or pubertal stages 1 to 5 (Figure 1) (15-17).

Stage	Female Breast Development	Male Genitalia Development	Pubic Hair (females and males)
1	Prepubertal	Prepubertal	Prepubertal
2	Bud with elevation of breast and papilla; enlargement of areola	Enlargement of testes and scrotum;	Sparse growth of long, slightly pigmented hair, straight or curled
3	Further enlargement of breast and areola	Enlargement of penis (lengthens first)	Darker, coarser, more curled
4	Areola and papilla form a secondary mound above the level of the breast	Increased size of penis with growth in breadth and development of glans; scrotum darker and larger, testes enlarge	Adult type hair, but covering small area, no spread to medial thigh surface
5	Mature	Adult	Adult in quantity and type

Figure 1. Pubertal Stages

Menarche, the term used to define the first menstrual cycle or episode of vaginal bleeding in females, generally occurs at pubertal stage 4; while pubertal stage 5 is used to define adult sexual maturity in both males and females. Despite earlier onset of secondary sexual characteristics, such as pubic hair, historically the median age at menarche has remained relatively stable - occurring at approximately 12 to 13 years-of-age in most females - across well-nourished populations in developed countries. Over the past 30 years, data from the U.S. NHANES has found no significant change in the median age at menarche, except among the non-Hispanic black population, which has a 5.5-month earlier median age at menarche than occurred previously.

Excessive weight gain during childhood is associated with earlier onset of puberty. Environmental factors, including socioeconomic conditions, nutrition, and access to preventive health care, may also influence the timing and progression of puberty.

By 15 years-of-age, 98% of females will have experienced menarche (18). In addition to a benchmark marking the beginning of reproductive life in females, both premature and delayed menarche appear to be associated with increased cardiovascular disease (CVD) risk (19-21). Women with prolonged and irregular menstrual cycles also appear to have higher risk for premature CVD and type 2 diabetes (T2D) (22,23).

Previous studies have taken into account pubertal changes in assessing lipid and lipoprotein levels in youth (24-30). It should be noted that youth of the same age, sex, and race show considerable variability in their degree of sexual maturation and somatic

growth. Thus, at all pubertal stages, chronological age can vary widely. This suggests that the use of age alone may be misleading when assessing the levels and changes in lipid levels in this population. In a longitudinal study that assessed pubertal stage at various ages, the levels of TC, low density-lipoprotein cholesterol (LDL-C), and non-HDL-C decreased in all groups during puberty (31). HDL-C decreased and triglyceride (TG) levels increased in males during puberty, while no changes were observed in females. For HDL-C, sex differences in the pattern of change emerged by pubertal stage 3 (31). Prior data has also suggested that HDL-C concentrations continue to decrease in males into early adulthood while remaining constant in females (32). Pubertal development should, therefore, be considered when determining criteria for initiation of lipid screening in youth; pre-pubertal (often before 9 years-of-age) and post-pubertal (typically after 17 years-of-age) screening might be useful despite current recommendations to screen between 9 to 11 years-of-age (31). For females who become pregnant, it is important to be aware of the additional changes in lipids that have been well-described (33).

EFFECT OF PREGNANCY ON LIPID DISORDERS

Management of dyslipidemia in adolescent and young adult females requires a thorough knowledge of lipid metabolism and physiologic changes that occur during pregnancy. Those who are considering pregnancy in the setting of a lipid disorder may benefit from preconception consultation with an obstetrician/maternal-fetal medicine specialist with knowledge of complex pregnancies to discuss the impact of pregnancy on maternal disease. If not seen prior to becoming pregnant, referral of those with severe dyslipidemia or FH is recommended early in pregnancy. Severe dyslipidemia has been associated with a variety of obstetric and maternal complications including preterm delivery, hypertension-related disorders of pregnancy, fetal growth restriction, increased fat deposition in the fetus, and maternal pancreatitis (34).

Physiologic changes that occur during pregnancy lead to an increase in plasma concentrations of lipids and lipoproteins. Maternal hyperlipidemia routinely occurs in the later part of pregnancy with levels of TG, very low-density lipoproteins (VLDL-C), LDL-C, and HDL-C increased compared to non-pregnant females (35). These changes are related to increased insulin resistance during pregnancy as well as increased production of estrogen (36). Given the expected increases seen in cholesterol during pregnancy and the limited treatment options that are available, routinely following lipid levels during pregnancy is not recommended. However, patients with severe hypertriglyceridemia who are at-risk of pancreatitis and those with FH who may develop symptomatic ASCVD during pregnancy are an exception and should be followed closely (37). Following delivery, cholesterol concentrations begin to decline with levels returning to baseline in most women by 6 weeks postpartum. However, some data suggest levels may remain elevated for as long as 20 weeks postpartum. Breastfeeding leads to decreases in TG levels, however HDL-C levels increase. The effect of breastfeeding on LDL-C levels is unclear (36).

SAFETY AND EFFICACY OF LIPID-LOWERING THERAPY WITH A RISK OF PREGNANCY

In addition to heart-healthy living, use of LLMs is currently recommended as a treatment option for females with moderate-to-severe dyslipidemia (39,40). When prescribing these medications, it is important to understand the potential risks of each drug class as well as each individual drug, and effects on reproductive health. While rare, most adverse events are similar for male and female youth (41).

Recommendations for use of LLMs, such as statins, in females of childbearing age should consider the potential of teratogenicity (33, 39). To date there have been two systematic reviews that evaluated statins and teratogenicity. Neither found evidence that statins cause congenital anomalies independent of concomitant medical conditions associated with their use (42,43). Of interest, in women with a prior history of pre-eclampsia use of pravastatin during subsequent pregnancy has shown promising results for preventing recurrence (44,45). Nonetheless, caution is advised when recommending the use of statins in females, including adolescent and young adult females.

Due to the current recommendation to avoid pregnancy while using most LLMs (including statins), an informative, developmentally appropriate discussion regarding contraceptive options is recommended prior to treatment of females of childbearing age. Most **women who plan to become pregnant should stop the statin 1 to 2 months before conception is attempted (39,46,47).**

If an adolescent or young adult female becomes pregnant while taking a LLM other than a bile acid sequestrant (e.g., colesevelam), best practice has been to immediately stop the LLM and the patient should be followed closely by an obstetrician in addition to a lipid specialist. LDL apheresis can be safely used during pregnancy and may be beneficial to some women.

It should be stated, however, that in 2021 the FDA requested revisions to the prescribing information about statin use during pregnancy, noting that contraindication of these drugs in all pregnant women is not appropriate. The FDA recommended removing this labeling, based upon the benefits statins may have in preventing serious or potentially fatal events in a small group of very high-risk pregnant patients. Removing the contraindication enables health care professionals and patients to make individual decisions about benefit and risk, especially for those at very high risk of heart attack or stroke, such as homozygous FH and females who have previously had a heart attack or stroke (47).

NON-STATIN THERAPIES

Lifestyle changes, including dietary modifications, are recommended for all individuals with lipid disorders and should be considered a cornerstone of lipid management in pregnancy as well. There are limited data, however, on use of non-statin medications to treat elevations in cholesterol and triglyceride during pregnancy. If any of the following medications are considered in an adolescent or woman of child-bearing age, the potential for pregnancy and relative risks must be taken into consideration.

Bile Acid Sequestrants

Despite reassurance of statin safety, only bile acid sequestrants are currently considered safe for use in treating LDL-C disorders during pregnancy and breastfeeding.

Ezetimibe

No data are available on use during pregnancy. Animal studies have found ezetimibe crosses the placenta. At levels significantly higher than those achieved with human doses, there appears to be a slightly increased risk of skeletal abnormalities in rats and rabbits. Therefore, this agent is not recommended for use during pregnancy. If used prior to pregnancy, ezetimibe should be discontinued prior to attempting to become pregnant (48).

PCSK9 Inhibitors (Monoclonal Evolocumab, Alirocumab and mRNA Therapy Inclisiran)

No data are available on use during pregnancy. An

observational trial of evolocumab in pregnant women with FH was terminated after being unable to enroll sufficient subjects (4 patients in 4 years; clinical trials.gov NCT02906124). PCSK9 inhibitors are not approved for use in pregnancy nor currently recommended (48).

Bempedoic acid

This drug should be discontinued when pregnancy is recognized, unless the benefits of therapy outweigh the potential risks to the fetus (49).

Evinacumab

No data are available on use during pregnancy. Based on animal studies, exposure during pregnancy may lead to fetal harm (49).

Lomitapide

This drug is not recommended during pregnancy due to concerns for fetal harm (49).

Fibrates

Limited data are available on use during pregnancy. Adverse outcomes from the use of fibrates during the second trimester have not been reported. However, such observations are based on case reports (50). Most reported use of fibrates (both gemfibrozil and fenofibrate) during pregnancy occurred in the second trimester, after embryogenesis occurs. Studies in animals have found no increased risk of congenital malformations (48).

Omega-3-Fatty Acid

Lifestyle modifications with increase in dietary omega-3-fatty acids appear to be safe during pregnancy. Prescription omega-3-fatty acids are not approved for use during pregnancy (48).

Volanesorsen

No data are available on use during pregnancy. If used prior to pregnancy, volanesoren should be discontinued one month before attempting conception (51). This drug is not approved for use in the U.S.

Plasmapheresis

In those at-risk of severe elevations in TG due to acquired (insulin resistance/diabetes) and genetic causes (FCS and MCS), case reports and reviews have reported use of plasmapheresis in those who develop pancreatitis. The procedure appears to be safe and has the advantage of quickly lowering TG levels (52,53).

LDL Apheresis

This procedure can be safely used during pregnancy and may be beneficial to some women with severely elevated lipids, such as FH (39).

SEXUAL ACTIVITY, RISK OF PREGNANCY AND SEXUAL HISTORY TAKING

Drugs such as statins are increasingly prescribed to females of childbearing age, including prior to the onset of sexual maturity. Since current guidelines still suggest avoidance or discontinuation of most LLMs during pregnancy, it is important for clinicians to consider the appropriate age at which a conversation regarding contraceptive options should be initiated. In addition to knowledge regarding pubertal development and reproductive ability, clinicians should have an awareness of current sexual practices amongst adolescents. According to the National Center for Health Statistics Reports, an estimated 55% of U.S. male and female teens have had sexual intercourse by 18 years-of-age; approximately 80% of teens used some form of contraception during their first episode of sex (54).

The proportion of youth who have had sexual intercourse increases rapidly throughout adolescence. In 2013, approximately 1% of 10-year-olds, 20% of 15-year-olds and 65% of 18-year-olds reported having had sexual intercourse (Figure 2).

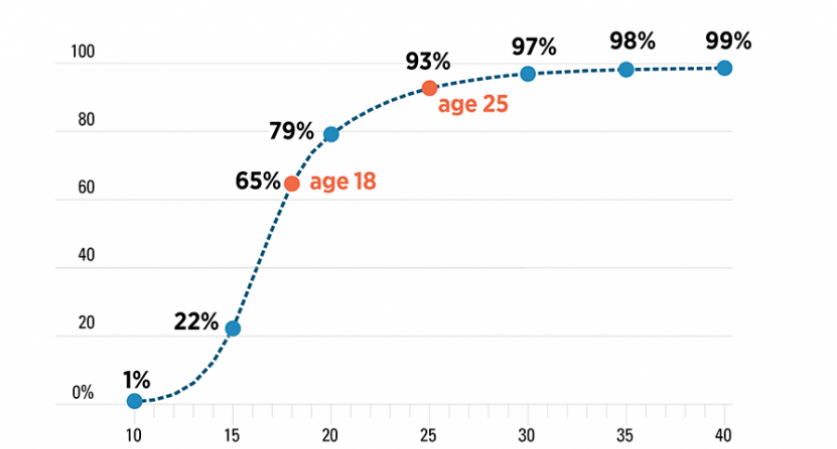

Figure 2. Percent of individuals 10-40 years-of-age who have had sexual intercourse. Modified from J. Philbin, Guttmacher Institute, unpublished data from the National Survey of Family Growth, 2013 (93).

For youth 11 years-of-age and older, the American Academy of Pediatrics (AAP) recommends healthcare providers obtain a developmentally-appropriate sexual history, including assessing risk of sexually transmitted infections (STIs) and pregnancy, and provision of appropriate screening, counseling, and, if needed, contraceptives options for adolescents during clinic visits (55).

An adolescent's sexual history should be updated regularly and conducted in a confidential and non-judgmental manner, re-addressing the needs for contraception, STI screening, and appropriate counseling regarding reduction of health risks related to sexual activity (56). Pregnancy testing should be conducted when appropriate or requested.

Key to effective history taking is an honest, caring, non-judgmental approach by the healthcare provider. Interviews should be conducted in a comfortable, matter-of-fact manner to encourage questions and to build trust. This can be accomplished by assessing the "5 Ps" of sexual history taking:

- **P**artners
- **P**revention of pregnancy
- **P**rotection from STIs
- Sexual **P**ractices
- **P**ast history of STIs and pregnancy

To encourage compliance, counseling should incorporate techniques of motivational interviewing (57).

Although there has been a decline in recent years, the pregnancy rate amongst adolescent females in the U.S. remains substantially higher than in other Western industrialized nations and racial/ethnic and geographic disparities in teen birth rates persist (58-62).

EFFECT OF CONTRACEPTIVE OPTIONS ON LIPOPROTEIN METABOLISM

While clinicians should review the effects on lipid levels when prescribing contraception, there are limited data to aid selection of a specific contraceptive method based upon the individual's underlying presumed or confirmed lipid disorder.

Review of the CDC *Summary Chart of US Medical Eligibility Criteria for Contraceptive Use* suggests avoidance of estrogen containing birth control as well as DMPA in individuals at increased risk of cardiovascular disease, which would include those with lipid disorders. Preferred methods of contraception for this vulnerable population would include the copper IUD, which contains no hormones, followed by a levonorgestrel containing IUD, implant, and progestin only contraceptive pills.

Although the impact of estrogen and progestin on lipid parameters has been well described, it is not known whether the hormone formulation or the means of administration of various contraceptive methods have any clinical significance either in women with normal baseline lipid levels or in those with lipid disorders (Table 1) (63). Furthermore, insufficient data are available in regard to the effect of various contraceptive methods when used in individuals with well-defined lipid disorders.

Table 1. The Effects of Contraceptive Methods on Lipids and Lipoproteins

Contraceptive Method	LDL-C	HDL-C	TG	Comments/References
Combined Oral Contraceptive Pill				
Estrogen	Decrease	Increase	Increase	For OCPs with an identical dose of estrogen, the choice and dose of the progestin component may affect net lipid changes (63,64)
Progestin	Increase	Decrease	Decrease	
Transdermal Patch	Decrease	Increase	Increase	(65)
Vaginal Ring	---	---	Increase	(66)
DMPA	Increase	Decrease	Neutral	(67,68)

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; DMPA = Depot medroxyprogesterone acetate

In general, combined oral contraceptives (COCs) raise TGs slightly. The effects on LDL-C and HDL-C are less predictable, but the effects are thought to be related to the dose of the ethinyl estradiol, the type of progestin, and health status of the patient (for example, obese versus not obese). Once OCPs are discontinued, lipid and lipoprotein levels appear to return to pre-treatment levels (64). If an oral contraceptive is preferred, the use of COCs that contain 35 mcg or less of estrogen is generally recommended for most adult women with controlled dyslipidemia.

Compared to COCs, transdermal and vaginal contraception have similar effects on lipid profiles. Barrier methods and IUDs are generally considered to be lipid neutral (65,66).

COCs have also been shown to increase plasma insulin and glucose levels and reduce insulin

sensitivity in women; however, these effects are negligible for current formulations and among women of normal weight without polycystic ovary syndrome (PCOS). For females who are overweight/obese and those with PCOS, potential adverse effects should be considered in the choice of contraceptive method (67-74).

SAFETY AND EFFICACY OF CONTRACEPTIVE OPTIONS IN ADOLESCENT AND YOUNG ADULT FEMALES

How does one determine which contraceptive is the best option for an adolescent or young adult female with dyslipidemia? From a practical point of view, this is largely dependent upon the individual's needs, preference, resources, and ability to adhere to the method chosen. Abstinence is 100% effective in preventing pregnancy and sexually transmitted infections, and is an important part of contraceptive counseling. Although adolescents should be encouraged to delay onset of sexual activity, adherence to abstinence in this age group is low. Therefore, healthcare providers are encouraged to discuss comprehensive sexual health and the risks/benefits of contraceptive options with all adolescents (56,75).

A review of the many options available for contraception is beyond the scope of this discussion. The safety and efficacy of contraceptive methods is also reviewed in the Endotext Chapter entitled "Contraception" (76). It is important to note that currently the most effective form of birth control is the contraceptive implant, followed by the IUD, and the progestin injection (Figures 3) (77).

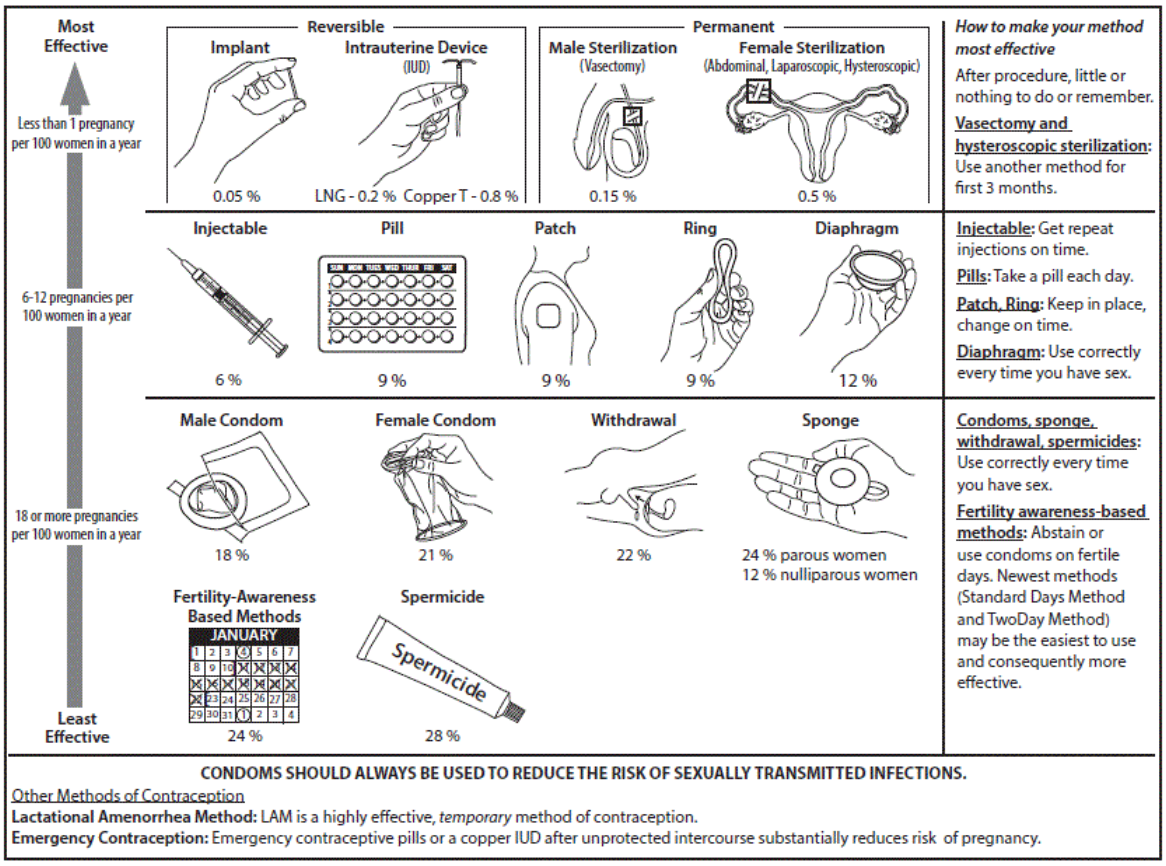

Figure 3. Effectiveness of Contraceptive Options. (Adapted from World Health Organization 2011 and Trussell, 2011. (78,79). * The percentages indicate the number of women out of every 100 who experienced an unintended pregnancy within the first year of typical use of each contraceptive method.

Given their efficacy, safety, and ease of use, in coordination with the American College of Obstetricians and Gynecologists, the AAP currently recommends long-acting reversible contraception (LARC) be considered first-line contraceptive choices for adolescents (56,80).

Key points for healthcare providers when recommending contraceptive methods:

- Depot medroxyprogesterone acetate (DMPA) and the contraceptive patch are highly effective methods of contraception that are much safer than pregnancy.
- It is appropriate to prescribe contraceptives or refer for IUD placement without first conducting a pelvic examination. Screenings for STIs, especially chlamydia, can be performed without a pelvic examination.
- If appropriate, consistent and correct use of condoms with every act of sexual intercourse should be encouraged.
- Physicians should have a working knowledge of the different combined hormonal methods and regimens for contraception and medical management of common conditions, such as acne, dysmenorrhea, and heavy menstrual bleeding.

- Adolescents with chronic illnesses and disabilities (estimated to be16 to 25% of adolescents) have similar sexual health and contraceptive needs as their healthy adolescent counterparts, although the medical illness may complicate contraceptive choices (56).

Healthcare providers who desire more information regarding contraception options for adolescent and young adult females, including those with medical conditions, are encouraged to consult the Centers for Disease Control and Prevention (CDC) U.S. Selected Practice Recommendations for Contraceptive Use (81,82).

HORMONAL CONTRACEPTIVE METHODS IN FEMALES WITH COMPLEX MEDICAL CONDITIONS

Aside from concerns regarding the effects of medications during unplanned pregnancy, recommendations for choice of contraceptive methods in females with primary lipid disorders should follow the same guidelines as outlined for age-appropriate females. Those with secondary dyslipidemia related to complicated, long-term medical conditions, such as chronic inflammatory diseases (e.g., rheumatoid arthritis, systemic lupus), diabetes, and HIV may require addition considerations prior to recommending use of a specific contraceptive method. The concurrent use of medications may also affect contraceptive choices. Table 2 provides a brief summary of the current guidelines to assist in clinical decision-making. For a more detailed discussion, a review of the US Selected Practice Recommendations (US SPR) for Contraceptive Use, 2016 is recommended (74-81).

Table 2. Summary of Classifications for Hormonal Contraceptive Methods and Intrauterine Devices

Condition	Cu-IUD	LNG-IUD	Implants	DMPA	POP	CHCs
Obesity						
a. BMI ≥30 kg/m^2	1	1	1	1	1	2
b. Menarche <18 years and BMI ≥30 kg/m^2	1	1	1	2	1	2
Cardiovascular Disease						
a. Multiple risk factors for ASCVD[a]	1	2	2*	3*	2*	3/4*
Hypertension[b]						
a. Adequately controlled hypertension	1*	1*	1*	2*	1*	3*
b. Elevated blood pressure levels (properly taken measurements)						
BP 140–159 mm Hg or DBP 90–99 mm Hg	1*	1*	1*	2*	1*	3*
BP ≥160 mm Hg or DBP ≥100 mm Hg	1*	2*	2*	3*	2*	4*
c. Vascular disease	1*	2*	2*	3*	2*	4*
Known thrombogenic mutations[c]	1*	2*	2*	2*	2*	4*
Rheumatic Diseases						
Systemic lupus erythematosus[d]						

a. Positive (or unknown) antiphospholipid antibodies		3*	3*		3*	4*
Initiation	1*			3*		
Continuation	1*			3*		
b. Severe thrombocytopenia		2*	2*		2*	2*
Initiation	3*			3*		
Continuation	2*			2*		
c. Immunosuppressive therapy		2*	2*		2*	2*
Initiation	2*			2*		
Continuation	1*			2*		
d. None of the above		2*	2*		2*	2*
Initiation	1*			2*		
Continuation	1*			2*		
Rheumatoid arthritis						
a. Receiving immunosuppressive therapy			1	2/3*	1	2
Initiation	2	2				
Continuation	1	1				
b. Not receiving immunosuppressive therapy	1	1	1	2	1	2
Reproductive Tract Infections and Disorders						
a. Irregular pattern without heavy bleeding	1		2	2	2	1
Initiation		1				
Continuation		1				
b. Heavy or prolonged bleeding (regular and irregular patterns)	2*		2*	2*	2*	1*
Initiation		1*				
Continuation		2*				
Severe dysmenorrhea	2	1	1	1	1	1
HIV						
High risk for HIV			1	1*	1	1
Initiation	2	2				
Continuation	2	2				
HIV infection[e]			1*	1*	1*	1*
Initiation	—	—				
Continuation	—	—				
a. Clinically well receiving ARV therapy			—	—	—	—
Initiation	1	1				
Continuation	1	1				

b. Not clinically well or not receiving ARV therapy			—	—	—	—
Initiation	2	2				
Continuation	1	1				
Endocrine Conditions						
Diabetes						
Non-insulin dependent and Insulin dependent[f]	1	2	2	2	2	2
Nephropathy, retinopathy, or neuropathy	1	2	2	3	2	3/4*
Hypothyroid	1	1	1	1	1	1
* Consult the respective appendix for each contraceptive method in the 2016 U.S. Medical Eligibility Criteria for Contraceptive Use for clarifications to the numeric categories.						
[a]Older age, smoking, diabetes, hypertension, low HDL, high LDL, or high triglyceride levels; [b]Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg are associated with increased risk for adverse health events as a result of pregnancy; [c]Factor V Leiden; prothrombin mutation; and protein S, protein C, and antithrombin deficiencies are associated with increased risk for adverse health events as a result of pregnancy; [d]This condition is associated with increased risk for adverse health events as a result of pregnancy; [d]For women with HIV infection who are not clinically well or not receiving ARV therapy, this condition is associated with increased risk for adverse health events as a result of pregnancy; [e]Insulin-dependent diabetes; diabetes with nephropathy, retinopathy, neuropathy, or diabetes with other vascular disease; or diabetes of >20 years' duration are associated with increased risk of adverse health events as a result of pregnancy; [f]Nonvascular disease Categories for classifying hormonal contraceptives and intrauterine devices 1 = A condition for which there is no restriction for the use of the contraceptive method. 2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks. 3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method. 4 = A condition that represents an unacceptable health risk if the contraceptive method is used. Modified from Curtis, 2016 (81,82).						

WHEN CAN A CONTRACEPTIVE METHOD BE INITIATED?

Same day initiation of a contraceptive, often referred to as a "quick start", should be considered when appropriate, since delayed initiation may represent a barrier. All contraceptive methods can be initiated at any time, including on the day of the visit, if there is reasonable certainty that the adolescent or young adult female is not pregnant. This can be ascertained via history (no intercourse since last menstrual period or less than 7 days from the first day of last menstrual

period) and a negative urine pregnancy test. In the setting of uncertainty regarding the possibility of pregnancy, initiation of COC, progestin only pills, and DMPA can proceed as the benefits are thought to outweigh the risks. Insertion of an IUD, however, should be avoided until the absence of pregnancy can be reasonably confirmed. https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Adolescent-Pregnancy-Contraception-and-Sexual-Activity?IsMobileSet=false

Although pregnancy tests are often performed before initiating contraception, it should be noted that the accuracy of qualitative urine pregnancy tests varies. Pregnancy detection rates can vary widely because of differences in test sensitivity and the timing of testing relative to missed menses (83,84). A history of starting a normal menstrual period within the last 7 days or a denial of sexual intercourse since the start of the last normal menstrual period may not always be reliable. In addition, a young adolescent female may not have undergone menarche or may have irregular cycles within the first several months of initiating menarche, making it difficult to use this measure to rule out pregnancy.

Prior to starting contraception, expectation of bleeding and possible menstrual changes associated with various methods should be reviewed.

For females in which there is an uncertainty about the risk of pregnancy, except for an IUD, the benefits of starting other contraceptive methods likely exceed any risk. A pregnancy test should be repeated in 2-4 weeks. Additional information is available in the CDC's U.S. Selected Practice Recommendations for Contraceptive Use.

SHOULD LABORATORY SCREENING AND PELVIC EXAMINATION BE PERFORMED PRIOR TO INITIATION OF HORMONE CONTRACEPTION?

As opposed to the general population, adolescent and young adult females with known dyslipidemia face a unique challenge. Machado and colleagues, noted dyslipidemia in 33% of 516 women (18-40 years-of-age), often accompanied by a history of smoking and an elevated BMI (85). Those with known medical problems or other special conditions might need additional examinations or tests before being considered appropriate candidates for a particular method of contraception.

All adolescent and young adult females at-risk of CVD should have their blood pressure measured before initiation of COCs to ensure there is no underlying hypertension that might be exacerbated by the medication. Measurements of weight and a calculated BMI at baseline is helpful in monitoring changes and offering timely counseling to those who might be concerned about weight change perceived to be associated with their contraceptive method.

For most healthy females, few examinations or tests are generally needed before initiation of most contraceptive methods. Research suggests that mandatory laboratory screening prior to initiation of contraceptive methods in this population can increase costs and may impose barriers to contraceptive access, critical in reducing unintended pregnancy (81,82,86). In general, laboratory tests, such as glucose, liver enzymes, hemoglobin and thrombogenic gene variants, pelvic examination and even screening for STD/HIV in the general population, are not recommended prior to initiation of treatment, since they do not contribute substantially to safe and effective use of the contraceptive method.

CURRENT RECOMMENDATIONS FOR MONITORING OF ADOLESCENT AND YOUNG ADULT WOMEN WITH DYSLIPIDEMIA DURING CONTRACEPTIVE USE

Guidelines for monitoring teenage girls with dyslipidemia during use of contraceptives are lacking. It seems reasonable, however, to measure fasting serum lipid levels within 3 months following initiation of a contraceptive; and less frequently once lipid parameters are stable. In those with an LDL-C 160 mg/dL or more, or multiple additional CVD risk factors (including smoking, diabetes, obesity, hypertension, TGs greater than 250 mg/dL, HDL-C less than 35 mg/dL, or a family history of premature coronary artery disease), use of alternative contraception method should be considered. Preferred methods of contraception for this at-risk population include the copper IUD, which contains no hormones, followed by a levonorgestrel containing IUD, implant, and progestin only contraceptive pills. All are equally acceptable. No major concerns have been raised with interactions between lipid lowering medication and contraception.

LEGAL CONCERNS

One of the common legal concerns in treating youth less than 18 years-of-age is that of confidentiality for care surrounding reproductive health. The AAP supports policies of informed consent and protection of confidentiality for adolescents seeking contraception and sexual healthcare services. Confidentiality is critical in all discussions, care recommendations and documentation of sexual identity, sexual practices, sexually transmitted infections (STIs), and contraceptive choices (56,87,88). These concepts are important, since limitations of confidentiality and consent are linked to lower use of contraceptives and higher adolescent pregnancy rates (89-92).

Over the past 30 years, in the U.S. states have expanded minors' authority to consent to health care, including care related to sexual activity. This trend reflects the 1977 U.S. Supreme Court ruling in *Carey v. Population Services International* that affirmed the constitutional right, in all states, to privacy for a minor to obtain contraceptives. The ruling also recognizes that while parental involvement is desirable, many minors will remain sexually active but may fail to seek reproductive advice or services if parental consent or acknowledged is required (93).

The majority of states have specific laws regarding a minor's consent to contraception. The Guttmacher report (93) on current state laws and policies found:

- 23 states and the District of Columbia explicitly allow all minors to consent to contraceptive services.
- 24 states explicitly permit minors to consent to contraceptive services in one or more circumstances.
- 4 states have no explicit policy on minors' authority to consent to contraceptive services.

For states without specific laws, best practice guidelines, federal statutes and federal case law may support minor confidentiality and consent. For example, family planning clinics funded by Title X of the federal Public Health Services Act (42 USC §§300–300a-6 [1970]) are required to provide confidential services to adolescents (94).

Even when a state has no relevant policy, case law or an explicit limitation, healthcare providers may provide medical care to a mature minor without parental consent, particularly if the state allows a minor to consent to related health services.

The Health Insurance Portability and Accountability Act (HIPAA) also specifically addresses minor confidentiality (95). Although HIPAA allows parents access to a minor's medical record as personal representatives, that access is denied when the minor is provided with confidentiality under state or other laws or when the parent agrees that the minor may have confidential care (96).

Therefore, the AAP recommends that pediatricians have clinic policies that explicitly outline applicable confidential services and that healthcare providers discuss (and document) confidentiality policies with all parents and adolescents. HIPAA also states that if there is no applicable state law about the rights of parents to access the protected health information of their children, pediatricians (or other licensed health professionals) may exercise their professional judgment in providing or denying parental access to the medical records. Providers are encouraged to include detailed documentation of the decision in the child's medical record (96).

Insurance, billing, and electronic health record systems create additional challenges, including an ability to maintain the confidentiality of visits, visit content, associated laboratory test results, and payment for the contraceptive method. For additional discussion of electronic health records, the AAP has published a policy statement on health information technology (97).

Although contraception services should be provided as a confidential service, adolescent females should be encouraged to involve parents or trusted adults whenever possible. In fact, many parents are supportive of minor consent and confidentiality for sexual health services (98,99). Adolescents who discuss sexuality and contraception with a parent or guardian are also more likely to use contraceptives consistently and are less likely to become pregnant (100,101).

For individuals who are sexually active, it is important to discuss and document a plan for pregnancy prevention. Dermatologists have extensive experience with risk monitoring in adolescents. Use of isotretinoin, a medication with known teratogenic potential, requires an FDA mandated pregnancy prevention program (iPLEDGE). In this program, females are required to undergo monthly pregnancy testing, and pharmacies, wholesalers and prescribers are all required to participate in a system of informed written consent, warning labels, database registration and monthly identification of contraceptive methods. Despite its attempts to prevent adverse outcomes, the efficacy of this approach is debated (102).

SUMMARY AND ADDITIONAL RESOURCES

For adolescent and young adult females who may benefit from use of lipid-lowering medication, it is important to consider the individual's stage of sexual maturation and sexual history in addition to the lipid disorder when making recommendation for contraception. For those who are sexually active, a comprehensive, developmentally appropriate discussion and documentation of a plan for reproductive health and pregnancy prevention is recommended. Most adolescents consider healthcare providers a highly reliable source of healthcare information. Establishing relationships with adolescents and families allow them to inquire about sensitive topics, such as sexuality and relationships, and to promote healthy decision-making. Several organizations provide excellent resources and extensive guidance in the appropriate use of contraceptive methods. With careful attention to confidentiality and reliable implementation of the individual plan for pregnancy prevention, healthcare providers can navigate the legal and ethical concerns while providing appropriate and compassionate care. When used cautiously in a supportive healthcare environment, lipid-lowering medications are safe and

effective in treating lipid disorders in adolescent and young adult females.

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REFERENCES

1. Levenson AE, de Ferranti SD. Familial Hypercholesterolemia. 2020 Feb 8. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 27809433.
2. Shah AS, Wilson DP. Genetic Disorders Causing Hypertriglyceridemia in Children and Adolescents. 2020 Jan 22. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 27809432.
3. Benuck I, Wilson DP, McNeal C. Secondary Hypertriglyceridemia. 2020 Jun 1. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 27809435.
4. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind BM. Lipid and lipoprotein distributions in white children ages 6-19 yr. The Lipid Research Clinics Program Prevalence Study. *J Chronic Dis.* 1981;34(1):27-39. doi:10.1016/0021-9681(81)90079-5
5. Lauer RM, Lee J, Clarke WR. Factors affecting the relationship between childhood and adult cholesterol levels: the Muscatine Study. *Pediatrics.* 1988;82(3):309-318.
6. Srinivasan SR, Wattigney W, Webber LS, Berenson GS. Race and gender differences in serum lipoproteins of children, adolescents, and young adults--emergence of an adverse lipoprotein pattern in white males: the Bogalusa Heart Study. *Prev Med.* 1991;20(6):671-684. doi:10.1016/0091-7435(91)90063-a
7. Twisk JW, Kemper HC, Mellenbergh GJ. Longitudinal development of lipoprotein levels in males and females aged 12-28 years: the Amsterdam Growth and Health Study. *Int J Epidemiol.* 1995;24(1):69-77. doi:10.1093/ije/24.1.69
8. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: data from the Third National Health and Nutrition Examination Survey. *Prev Med.* 1998;27(6):879-890. doi:S0091-7435(98)90376-0
9. Ford ES, Mokdad AH, Ajani UA. Trends in risk factors for cardiovascular disease among children and adolescents in the United States. *Pediatrics.* 2004;114(6):1534-1544. doi:114/6/1534
10. Dai S, Fulton JE, Harrist RB, Grunbaum JA, Steffen LM, Labarthe DR. Blood lipids in children: age-related patterns and association with body-fat indices: Project HeartBeat! *Am J Prev Med.* 2009;37(1 Suppl):56. doi:10.1016/j.amepre.2009.04.012.
11. Kit BK, Carroll MD, Lacher DA, Sorlie PD, DeJesus JM, Ogden C. Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. *JAMA.* 2012;308(6):591-600. doi:10.1001/jama.2012.9136
12. Mellerio H, Alberti C, Druet C, et al. Novel modeling of reference values of cardiovascular risk factors in children aged 7 to 20 years. *Pediatrics.* 2012;129(4):1020. doi:10.1542/peds.2011-0449
13. Drash A, Hengstenberg F. The identification of risk factors in normal children in the development of arteriosclerosis. *Ann Clin Lab Sci.* 1972;2(5):348-359.
14. Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. *JAMA Pediatr.* 2015;169(3):272-279. doi:10.1001/jamapediatrics.2014.3216

15. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child.* 1969;44(235):291-303. doi:10.1136/adc.44.235.291
16. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child.* 1970;45(239):13-23. doi: 0.1136/adc.45.239.13
17. Beccuti G, Ghizzoni L. Normal and abnormal puberty. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext.* MDText.com, Inc; South Dartmouth, MA: 2015.
18. ACOG Committee Opinion No. 651: Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. *Obstet Gynecol.* 2015;126(6):e143-e146. doi:10.1097/AOG.0000000000001215
19. Lakshman R, Forouhi NG, Sharp SJ, et al. Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab.* 2009;94(12):4953-4960. doi:10.1210/jc.2009-1789
20. Rudra CL, Williams MA. BMI as a modifying factor in the relations between age at menarche, menstrual cycle characteristics, and risk of preeclampsia. *Gynecol Endocrinol.* 2005;21(4):200-205. doi:P2G017365M63654M
21. Freedman DS, Khan LK, Serdula MK, et al. The relation of menarcheal age to obesity in childhood and adulthood: the Bogalusa heart study. *BMC Pediatr.* 2003;3:3-3. Epub 2003 Apr 30. doi:1471-2431-3-3
22. Solomon CG, Hu FB, Dunaif A, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. *J Clin Endocrinol Metab.* 2002;87(5):2013-2017. doi:10.1210/jcem.87.5.8471
23. Veltman-Verhulst SM, van Rijn BB, Westerveld HE, et al. Polycystic ovary syndrome and early-onset preeclampsia: reproductive manifestations of increased cardiovascular risk. *Menopause.* 2010;17(5):990-996. doi:10.1097/gme.0b013e3181ddf705
24. Porkka KV, Viikari JS, Rönnemaa T, Marniemi J, Akerblom HK. Age and gender specific serum lipid and apolipoprotein fractiles of Finnish children and young adults. The Cardiovascular Risk in Young Finns Study. *Acta Paediatr.* 1994;83(8):838-848. doi:10.1111/j.1651-2227.1994.tb13155.x
25. Armstrong N, Balding J, Gentle P, Kirby B. Serum lipids and blood pressure in relation to age and sexual maturity. *Ann Hum Biol.* 1992;19(5):477-487. doi:10.1080/03014469200002312
26. Morrison JA, Laskarzewski PM, Rauh JL, et al. Lipids, lipoproteins, and sexual maturation during adolescence: the Princeton maturation study. *Metabolism.* 1979;28(6):641-649. doi:0026-0495(79)90017-9
27. Altwaijri YA, Day RS, Harrist RB, Dwyer JT, Ausman LM, Labarthe DR. Sexual maturation affects diet-blood total cholesterol association in children: Project HeartBeat! *Am J Prev Med.* 2009;37(1 Suppl):65. doi:10.1016/j.amepre.2009.04.007
28. Srinivasan SR, Elkasabany A, Berenson GS. Distribution and correlates of serum high-density lipoprotein subclasses (LpA-I and LpA-I:A-II) in children from a biracial community. The Bogalusa Heart Study. *Metabolism.* 1998;47(6):757-763. doi:S0026-0495(98)90042-7
29. Tell GS, Mittelmark MB, Vellar OD. Cholesterol, high density lipoprotein cholesterol and triglycerides during puberty: the Oslo Youth Study. *Am J Epidemiol.* 1985;122(5):750-761. doi:10.1093/oxfordjournals.aje.a114158
30. Sprecher DL, Morrison JA, Simbartl LA, et al. Lipoprotein and apolipoprotein differences in black and white girls. The National Heart, Lung, and Blood Institute Growth and Health Study. *Arch Pediatr Adolesc Med.* 1997;151(1):84-90. doi:10.1001/archpedi.1997.02170380088014
31. Eissa MA, Mihalopoulos NL, Holubkov R, Dai S, Labarthe DR. Changes in fasting lipids during puberty. *J Pediatr.* 2016;170:199-205. doi:S0022-3476(15)01371-2
32. Kreisberg RA, Kasim S. Cholesterol metabolism and aging. *Am J Med.* 1987;82(1B):54-60. doi:0002-9343(87)90272-5
33. Grimes SB, Wild R. Effect of pregnancy on lipid metabolism and lipoprotein levels. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext.* MDText.com, Inc; South Dartmouth, MA: 2018.
34. Mukherjee M. Dyslipidemia in pregnancy, expert analysis. American College of Cardiology web site. Updated 2014. Accessed March 8, 2022. https://www.acc.org/latest-in-cardiology/articles/2014/07/18/16/08/dyslipidemia-in-pregnancy
35. Lippi G, Albiero A, Montagnana M, et al. Lipid and lipoprotein profile in physiological pregnancy. *Clin Lab.* 2007;53(3-4):173-177.
36. Maternal physiology. In: Cunningham FG, Leveno KJ, Bloom SL, et al, eds. *Williams obstetrics*. 25th ed. McGraw-Hill Education Medical; 2018:49-78.
37. Gupta M, Liti B, Barrett C, Thompson PD, Fernandez AB. Prevention and Management of Hypertriglyceridemia-Induced Acute Pancreatitis During Pregnancy: A Systematic Review. Am J Med. 2022 Jun;135(6):709-714. doi: 10.1016/j.amjmed.2021.12.006. Epub 2022 Jan 23. PMID: 35081380.
38. Gunderson EP, Chiang V, Pletcher MJ, et al. History of gestational diabetes mellitus and future risk of atherosclerosis in mid-life: the Coronary Artery Risk Development in Young Adults study. *J Am Heart Assoc.* 2014;3(2):e000490. doi:10.1161/JAHA.113.000490

39. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol. 2019 Jun 25;73(24):3237-3241]. J Am Coll Cardiol. 2019;73(24):e285-e350. doi:10.1016/j.jacc.2018.11.003
40. de Ferranti SD, Steinberger J, Ameduri R, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation.* 2019;139(13):e603-e634. doi:10.1161/CIR.0000000000000618
41. Miller, ML, Wright, CC, Rodrigues B, et al. Use of lipid lowering medications in youth. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext.* MDText.com, Inc; South Dartmouth, MA: 2020.
42. Karalis DG, Hill AN, Clifton S, Wild RA. The risks of statin use in pregnancy: a systematic review. *J Clin Lipidol.* 2016;10(5):1081-1090. doi:S1933-2874(16)30234-3
43. Kusters DM, Hassani Lahsinoui H, van de Post, J. A., et al. Statin use during pregnancy: a systematic review and meta-analysis. *Expert Rev Cardiovasc Ther.* 2012;10(3):363-378. doi:10.1586/erc.11.196
44. Costantine MM, Cleary K, Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric--Fetal Pharmacology Research Units Network*. Pravastatin for the prevention of preeclampsia in high-risk pregnant women. *Obstet Gynecol.* 2013;121(2 Pt 1):349-353. doi:10.1097/AOG.0b013e31827d8ad5
45. Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. *Am J Obstet Gynecol*. 2016;214(6):720.e1-720.e17. doi:10.1016/j.ajog.2015.12.038
46. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract.* 2017;23(Suppl 2):1-87. doi:10.4158/EP171764.APPGL
47. Federal Drug Administration. Statins: Drug Safety Communication - FDA requests removal of strongest warning against using cholesterol-lowering statins during pregnancy. FDA web site. Updated 2021. Accessed Mar 8, 2022. https://www.fda.gov/safety/medical-product-safety-information/statins-drug-safety-communication-fda-requests-removal-strongest-warning-against-using-cholesterol.
48. Reprotox - online database for medication and pregnancy/lactation
49. Writing Committee, Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Covington AM, DePalma SM, Minissian MB, Orringer CE, Smith SC Jr, Waring AA, Wilkins JT. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022 Oct 4;80(14):1366-1418. doi: 10.1016/j.jacc.2022.07.006. Epub 2022 Aug 25. PMID: 36031461.
50. Wong B, Ooi TC, Keely E. Severe gestational hypertriglyceridemia: A practical approach for clinicians. Obstet Med. 2015 Dec;8(4):158-67. doi: 10.1177/1753495X15594082. Epub 2015 Aug 21. PMID: 27512474; PMCID: PMC4935053.
51. Kolovou G, Kolovou V, Katsiki N. Volanesorsen: A New Era in the Treatment of Severe Hypertriglyceridemia. J Clin Med. 2022 Feb 13;11(4):982. doi: 10.3390/jcm11040982. PMID: 35207255; PMCID: PMC8880470.
52. Cruciat G, Nemeti G, Goidescu I, Anitan S, Florian A. Hypertriglyceridemia triggered acute pancreatitis in pregnancy - diagnostic approach, management and follow-up care. Lipids Health Dis. 2020 Jan 4;19(1):2. doi: 10.1186/s12944-019-1180-7. PMID: 31901241; PMCID: PMC6942404.
53. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Hypertriglyceridemia-induced pancreatitis: updated review of current treatment and preventive strategies. Clin J Gastroenterol. 2018 Dec;11(6):441-448. doi: 10.1007/s12328-018-0881-1. Epub 2018 Jun 19. PMID: 29923163.
54. Abma JC, Martinez GM. Sexual activity and contraceptive use among teenagers in the United States, 2011-2015. *Natl Health Stat Report.* 2017;(104):1-23.
55. Hagan JF, Shaw JS, Duncan PM. *Bright futures*: *Guidelines for health supervision of infants, children, and adolescents.* 4th ed. American Academy of Pediatrics; 2017.
56. American Academy of Pediatrics Committee on Adolescence. Contraception for adolescents. *Pediatrics.* 2014;134(4):e1244-e1256.. doi:10.1542/peds.2014-2299
57. Reno H, Park I, Workowski K, Machefsky A, Bachmann L. A guide to taking a sexual history. Centers for Disease Control and Prevention (CDC) web site. Reviewed

January 14, 2022. Accessed February 24, 2022. https://www.cdc.gov/std/treatment/sexualhistory.pdf.
58. Sedgh G, Finer LB, Bankole A, Eilers MA, Singh S. Adolescent pregnancy, birth, and abortion rates across countries: levels and recent trends. *J Adolesc Health.* 2015;56(2):223-230. doi:S1054-139X(14)00387-5
59. Romero L, Pazol K, Warner L, et al. Reduced disparities in birth rates among teens aged 15-19 years - United States, 2006-2007 and 2013-2014. *MMWR Morb Mortal Wkly Rep.* 2016;65(16):409-414. doi:10.15585/mmwr.mm6516a1
60. Lindberg L, Santelli J, Desai S. Understanding the Decline in Adolescent Fertility in the United States, 2007-2012. *J Adolesc Health.* 2016;59(5):577-583. doi:S1054-139X(16)30172-0
61. Martin JA, Hamilton BE, Osterman MJ, Driscoll AK, Drake P. Births: Final data for 2017. *National Vital Statistics Reports.* 2018;67(8):1-50. https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf.
62. Santelli JS, Lindberg LD, Finer LB, Singh S. Explaining recent declines in adolescent pregnancy in the United States: the contribution of abstinence and improved contraceptive use. *Am J Public Health.* 2007;97(1):150-156. doi:AJPH.2006.089169
63. ACOG Committee on Practice Bulletins-Gynecology. ACOG Practice Bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions. *Obstet Gynecol.* 2006;107(6):1453-1472. doi:107/6/1453
64. Fotherby K. Oral contraceptives and lipids. *BMJ.* 1989;298(6680):1049-1050. doi:10.1136/bmj.298.6680.1049
65. Elkind-Hirsch KE, Darensbourg C, Ogden B, Ogden LF, Hindelang P. Contraceptive vaginal ring use for women has less adverse metabolic effects than an oral contraceptive. *Contraception.* 2007;76(5):348-356. doi:S0010-7824(07)00350-2
66. Guazzelli CA, Barreiros FA, Barbosa R, Torloni MR, Barbieri M. Extended regimens of the contraceptive vaginal ring versus hormonal oral contraceptives: effects on lipid metabolism. *Contraception.* 2012;85(4):389-393. doi:10.1016/j.contraception.2011.08.014
67. Cheang KI, Essah PA, Sharma S, Wickham EP,3rd, Nestler JE. Divergent effects of a combined hormonal oral contraceptive on insulin sensitivity in lean versus obese women. *Fertil Steril.* 2011;96(2):353-359.e1. doi:10.1016/j.fertnstert.2011.05.039
68. Adeniji AA, Essah PA, Nestler JE, Cheang KI. Metabolic effects of a commonly used combined hormonal oral contraceptive in women with and without polycystic ovary syndrome. *J Womens Health.* 2016;25(6):638-645. doi:10.1089/jwh.2015.5418
69. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N Engl J Med.* 1991;325(17):1196-1204. doi:10.1056/NEJM199110243251702
70. Walsh BW, Sacks FM. Effects of low dose oral contraceptives on very low density and low density lipoprotein metabolism. *J Clin Invest.* 1993;91(5):2126-2132. doi:10.1172/JCI116437
71. Creasy GW, Fisher AC, Hall N, Shangold GA. Transdermal contraceptive patch delivering norelgestromin and ethinyl estradiol. Effects on the lipid profile. *J Reprod Med.* 2003;48(3):179-186.
72. Tuppurainen M, Klimscheffskij R, Venhola M, Dieben TO. The combined contraceptive vaginal ring (NuvaRing) and lipid metabolism: a comparative study. *Contraception.* 2004;69(5):389-394. doi:S0010782404000241
73. Kongsayreepong R, Chutivongse S, George P, et al. A multicentre comparative study of serum lipids and apolipoproteins in long-term users of DMPA and a control group of IUD users. World Health Organization. Task Force on Long-Acting Systemic Agents for Fertility Regulation Special Programme of Research, Development and Research Training in Human Reproduction. *Contraception.* 1993;47(2):177-191. doi:0010-7824(93)90090-T
74. Westhoff C. Depot medroxyprogesterone acetate contraception. Metabolic parameters and mood changes. *J Reprod Med.* 1996;41(5 Suppl):401-406.
75. American Academy of Pediatrics. Contraception Explained: Options for Teens & Adolescents. HealthyChildren.org web site. Updated 2020. Accessed Feb 24, 2022. https://www.healthychildren.org/English/ages-stages/teen/dating-sex/Pages/Birth-Control-for-Sexually-Active-Teens.aspx.
76. Horvath S, Schreiber CA, Sonalkar S. Contraception. 2018 Jan 17. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, Dungan K, Hershman JM, Hofland J, Kalra S, Kaltsas G, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, Morley JE, New M, Purnell J, Sahay R, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 25905371.
77. Horvath S, Schreiber CA, Sonalkar S. Contraception. In: Feingold KR, Anawalt B, Boyce A, et al, eds. *Endotext.* MDText.com, Inc; South Dartmouth, MA: 2018.

78. World Health Organization, Johns Hopkins Bloomberg School of Public Health. *Family planning: a global handbook for providers (2018 update): evidence-based guidance developed through worldwide collaboration.* 3rd ed. World Health Organization; 2018.
79. Trussell J. Contraceptive failure in the United States. *Contraception.* 2011;83(5):397-404. doi:10.1016/j.contraception.2011.01.021
80. Committee on Practice Bulletins-Gynecology, Long-Acting Reversible Contraception Work Group. Practice Bulletin No. 186: Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol.* 2017;130(5):e251-e269. doi:10.1097/AOG.0000000000002400
81. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep.* 2016;65(4):1-66. doi:10.15585/mmwr.rr6504a1
82. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep.* 2016;65(3):1-103. doi:10.15585/mmwr.rr6503a1
83. Cole LA. Human chorionic gonadotropin tests. *Expert Rev Mol Diagn.* 2009;9(7):721-747. doi:10.1586/erm.09.51
84. Wilcox AJ, Baird DD, Dunson D, McChesney R, Weinberg CR. Natural limits of pregnancy testing in relation to the expected menstrual period. *JAMA.* 2001;286(14):1759-1761. doi:jbr10110
85. Machado RB, Bernardes CR, de Souza IM, Santana N, Morimoto M. Is lipid profile determination necessary in women wishing to use oral contraceptives? *Contraception.* 2013;87(6):801-805. doi:S0010-7824(12)01034-7
86. Tepper NK, Steenland MW, Marchbanks PA, Curtis KM. Laboratory screening prior to initiating contraception: a systematic review. *Contraception.* 2013;87(5):645-649. doi:S0010-7824(12)00736-6
87. Christopher BA, Pagidipati NJ. Clinical updates in women's health care summary: evaluation and management of lipid disorders: primary and preventive care review. Obstet Gynecol. 2019;133(3):609. doi:10.1097/AOG.0000000000003139.
88. Ford C, English A, Sigman G. Confidential health care for adolescents: position paper for the Society for Adolescent Medicine. *J Adolesc Health.* 2004;35(2):160-167. doi:S1054-139X(04)00086-2
89. Reddy DM, Fleming R, Swain C. Effect of mandatory parental notification on adolescent girls' use of sexual health care services. *JAMA.* 2002;288(6):710-714. doi:joc11794
90. Zabin LS, Stark HA, Emerson MR. Reasons for delay in contraceptive clinic utilization. Adolescent clinic and nonclinic populations compared. *J Adolesc Health.* 1991;12(3):225-232. doi:0197-0070(91)90015-E
91. Zavodny M. Fertility and parental consent for minors to receive contraceptives. *Am J Public Health.* 2004;94(8):1347-1351. doi:94/8/1347
92. Lehrer JA, Pantell R, Tebb K, Shafer MA. Forgone health care among U.S. adolescents: associations between risk characteristics and confidentiality concern. *J Adolesc Health.* 2007;40(3):218-226. doi:S1054-139X(06)00375-2
93. Guttmacher Institute. An Overview of Consent to Reproductive Health Services by Young People. Guttmacher Institute web site. Updated 2022. Accessed Feb 24, 2022. https://www.guttmacher.org/state-policy/explore/overview-minors-consent-law
94. Center for Adolescent Health & the Law. *State minor consent laws: A summary.* 3rd ed. Chapel Hill, NC: Center for Adolescent Health & the Law; 2010.
95. The Health Insurance Portability and Accountability Act of 1996 (HIPA), Pub. L. No. 104-191, 110 Stat. 1936. 1996
96. English A, Ford CA. The HIPAA privacy rule and adolescents: legal questions and clinical challenges. *Perspect Sex Reprod Health.* 2004;36(2):80-86. doi:368004
97. Council on Clinical Information Technology. Health information technology and the medical home. *Pediatrics.* 2011;127(5):978-982. doi:10.1542/peds.2011-0454
98. Dempsey AF, Singer DD, Clark SJ, Davis MM. Adolescent preventive health care: what do parents want? *J Pediatr.* 2009;155(5):689-94.e1. doi:10.1016/j.jpeds.2009.05.029
99. Jones RK, Purcell A, Singh S, Finer LB. Adolescents' reports of parental knowledge of adolescents' use of sexual health services and their reactions to mandated parental notification for prescription contraception. *JAMA.* 2005;293(3):340-348. doi:293/3/340
100. Amialchuk A, Gerhardinger L. Contraceptive use and pregnancies in adolescents' romantic relationships: role of relationship activities and parental attitudes and communication. *J Dev Behav Pediatr.* 2015;36(2):86-97. doi:10.1097/DBP.0000000000000125
101. Crosby RA, DiClemente RJ, Wingood GM, et al. Low parental monitoring predicts subsequent pregnancy among African-American adolescent females. *J Pediatr Adolesc Gynecol.* 2002;15(1):43-46. doi:S1083318801001383
102. Abroms L, Maibach E, Lyon-Daniel K, Feldman SR. What is the best approach to reducing birth defects associated with isotretinoin? *PLoS Med.* 2006;3(11):e483. doi: 10.1371/journal.pmed.0030483