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TRUST CLINICAL GUIDELINE

Guideline for Using Lipid Lowering Therapy in Pregnancy

Overview

This guideline is to support the management of people at childbearing age who are trying to conceive, are pregnant or breast feeding, and who are on, or require, lipid lowering therapy. There are no national guidelines, and this cohort are generally excluded from research trials contributing to poor outcomes for cardiovascular disease in women. The guideline aims to support all clinicians to manage these patients, although the care will mainly be provided by maternal medicine and lipidology services. By producing pan-Sussex guidance the aim is to ensure all clinicians can identify, counsel, and refer this patient cohort in a timely manner and support specialist services by providing guidance for a structured approach pan-Sussex.

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Author/further information	Dr Kate Shipman, Consultant Lipidologist UHSx.
Guideline version	Clinical Guideline, with suggested Pathway Version 1.0
Related policies	N/A
Related protocols/procedures	N/A
Standards	NICE NG238, CG71, MHRA (use of medicines in pregnancy and breast feeding)
Superseded documents	N/A
Review due	January 2028

Approval		
Medical Governance Committee	Date approved:	19/11/2024
Sussex Area Prescribing Committee	Date approved:	30/07/2024
Consultation as relevant		
Circulated with maternal medicine, pharmacy, lipid and cardiovascular colleagues.	Date approved:	Prior to application to APC (2024)
Ratification		
Clinical Document Approval Group	Date approved:	27/1/2025

Contents

1. Introduction

The introduction of new classes of lipid lowering agents, accumulation of safety data and poor outcomes for women secondary to atherosclerotic heart disease has led to the critical examination of how we treat dyslipidaemias and cardiovascular risk in pregnancy (see Figure 1).

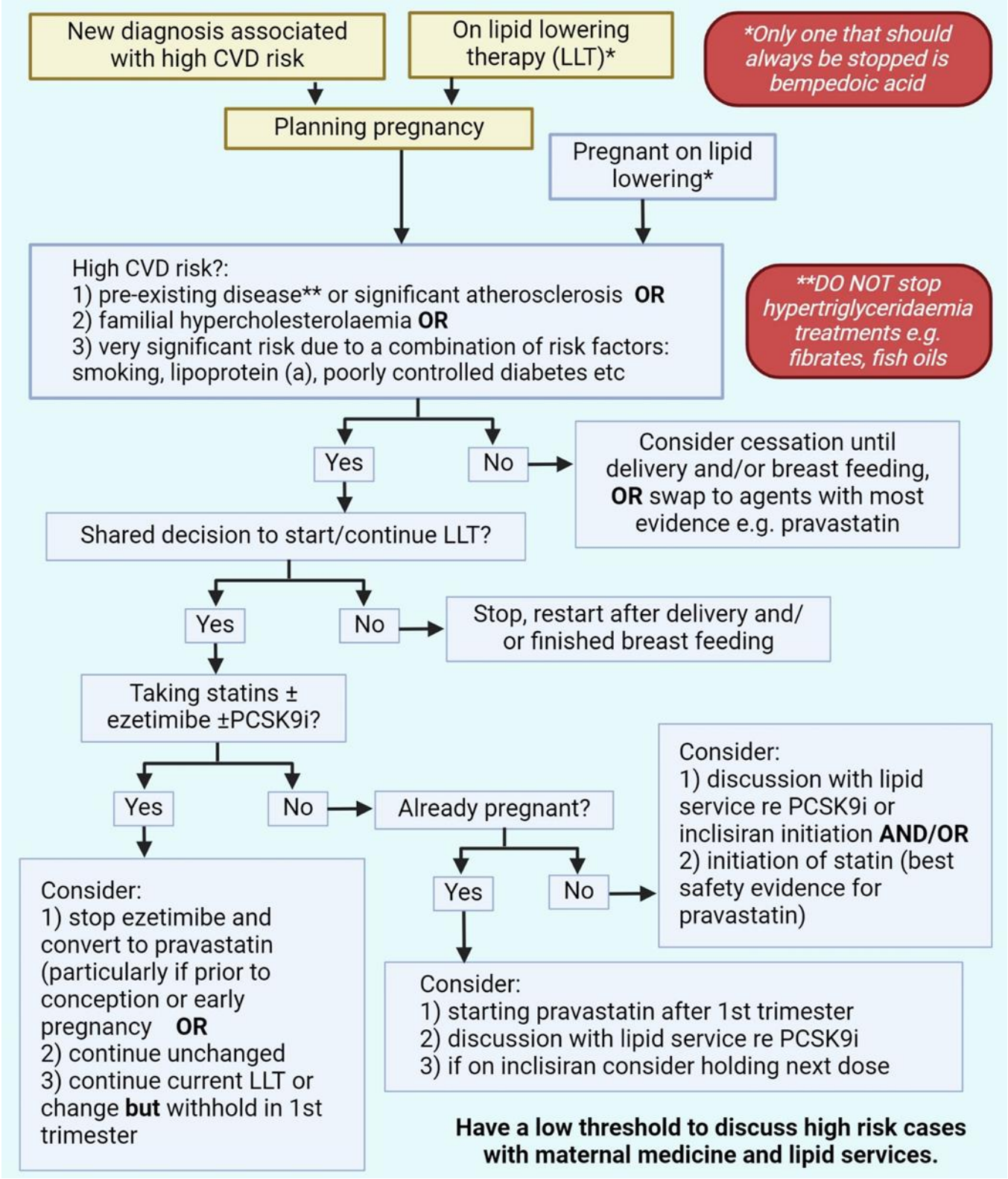


Figure 1: Flow Chart to Summarise the approach to Lipid Lowering Therapy in Pregnancy Planning/Management in People with High Cardiovascular Disease (CVD) Risk.
(Created using Biorender.com)

Background

There is a physiological increase in plasma concentrations of cholesterol and triglycerides during normal pregnancy with a linear association between triglycerides and adverse pregnancy outcomes and complications [1, 2]. Changes in fat metabolism relate to delivery of nutrients to the feto-placental unit to an extent, but excessive fat intake is not recommended [3]. Maternal lipid targets are reported in Table 1, but there is no evidence that pharmacologically treating to these targets improves pregnancy outcomes [4]:

Table 1: Lipid targets during pregnancy associated with optimum outcomes [4]

Lipid test (mmol/L)	Early pregnancy	Middle pregnancy
Total cholesterol	<5.64	<7.50
Triglycerides	<1.95	<3.56
HDL	>1.23	>1.41
LDL*	<3.27	<4.83

*no methods in paper (results from hospital labs from routine care)

Blood lipid levels remain elevated for at least one month following the birth of the baby, although triglyceride concentrations can fall more rapidly in individuals who breastfeed. Checking a lipid profile should normally be delayed for at least 2-3 months following delivery.

Individuals with pre-existing dyslipidaemias may exhibit extreme elevations which can be associated with complications. In the case of severe hypertriglyceridaemia there is an increased risk of acute pancreatitis and skin manifestations (eruptive xanthoma, a maculopapular rash, that can be widely distributed and intensely itchy). Atherosclerotic complications have significant impact on both pregnancy and the woman's outcome long term [5].

2. Recommendations

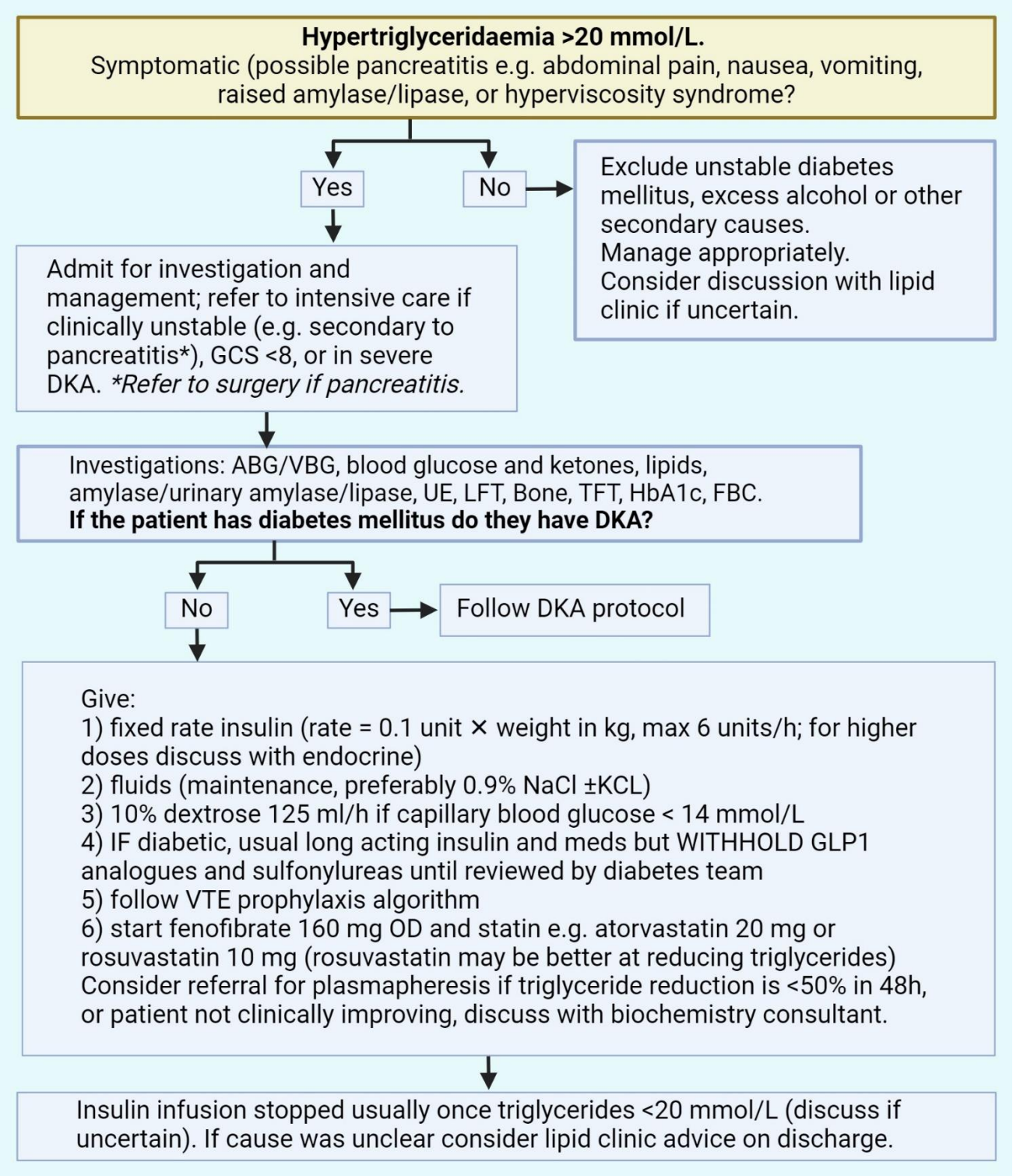
2.1 Pregnancy and familial hypercholesterolaemia

An otherwise healthy woman with familial hypercholesterolaemia (FH) should not be discouraged from becoming pregnant or breastfeeding their baby. However, all women with FH who are of childbearing age should be aware of the need for pre-pregnancy counselling prior to embarking on a pregnancy, and what they should do if they have an unplanned pregnancy. **Pregnant women with FH** should be under the shared care of specialists e.g. maternal medicine obstetrician / obstetric physician. All individuals should have a baseline ECG.

2.2 Pregnancy and hypertriglyceridaemia

With respect to the treatment of severe hypertriglyceridaemia during pregnancy, with or without pancreatitis, there are very limited data for treatment modalities (see below - Triglyceride reducing medicines). In very severe hypertriglyceridaemia (Familial Chylomicronaemia Syndrome), diabetes mellitus is often a co-morbidity, and improving diabetic control is a critical first step**. Limiting fat intake, glycaemic control and increasing lipoprotein lipase activity, e.g. with Fenofibrate,** are the mainstay of management (see Figure 2) [6].

Figure 2: Management of Hypertriglyceridemia in Adult In-patients; adapted from Guy's and St Thomas' Clinical Guideline (Integrated Care Pathway V 1.1).
(Created using Biorender.com)



2.3 Pregnancy and lipid-lowering medication

No medication should be stopped automatically due to pregnancy.
Lipid-lowering drug therapy should be consented carefully
when starting in women of child-bearing age (see Table 2).

The maternal medicine network can provide support and guidance for medication use in pregnancy. The team can be accessed for pre-pregnancy counselling or for referral/advice for pregnancy by emailing uhsussex.sussexmmc@nhs.net or by contacting the maternal medicine consultants at each site through antenatal clinic. Also consider discussion with lipid services and cardiology if appropriate. A summary of the following medication information is found in table 2.

- **LDL-cholesterol reducing medicines**

Statins
Recently published meta-analyses, found no evidence for congenital abnormalities with statin usage [7, 8]. There may be a signal for spontaneous miscarriages in the first trimester, but this may be because the women on statins had other risk factors for miscarriage, e.g. significant co-morbidities and higher age, and this was only seen in cohort studies (i.e. exclusion of these studies and only inclusion of randomised controlled trials (RCT) found no significant risk) [7].

One of the largest RCTs so far is a pre-eclampsia trial with pravastatin, started at 35-37 weeks until week 41 [9]. High risk warnings have been removed in recent years, such as the FDA, but statins are not yet recommended in pregnancy [5, 10]. One suggestion is that as uncertainty remains then reserving statins to the 2nd and 3rd trimester would most likely be a beneficial strategy with the lowest risk, and the most safety evidence exists for pravastatin [7]. Women to particularly consider continuing therapy in (throughout, or from the 2nd trimester onwards) include familial hypercholesterolaemia (FH) and secondary prevention patients for example.

No studies have looked at maternal safety secondary to stopping statins due to pregnancy. The FH survival data is however poor for women, the hypothesis being the lack of treatment during pregnancy causing significantly higher lifetime risk [11]. There is excellent safety data for statins in childhood [12].

Ezetimibe
There are no human data of ezetimibe in pregnancy, but animal studies have demonstrated no effects on fertility, embryofetal development, birth or postnatal development. Due to lack of systemic effects, there is no evidence that this drug must be stopped and therefore discuss on a case-by-case basis.

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)
Biologics (antibodies) in general are permitted during pregnancy (no placental transfer). There is a published case report of evolocumab (started at 28 weeks) with no apparent complications [13]. Therefore, do not stop and potentially consider starting (instead of other medications) in secondary prevention patients who are eligible, for example, if choose to stop statins for the duration of pregnancy (based on the indirect evidence of safety with other biologic medications).

Inclisiran

There has been one case reported to Novartis of a pregnant woman having exposure for approximately 2 months with inclisiran with no adverse effects. Inclisiran is only present in the blood for 48 hours after injection and is targeted to the liver. Theoretically therefore one could discuss treatment prior to conception of a single dose (40% reduction of LDL at 9 months) in high-risk patients where the plan is to stop the statins for early pregnancy, however there are no data for this approach and the licence is for secondary prevention only when LDL is ≥2.6 mmol/L (i.e. not an option for high-risk primary prevention) and they should be counselled to avoid becoming pregnant for 48 hours after the injection (at which point no drug is circulating in the maternal blood stream).

Bempedoic acid
There are no human data and recommendations are to avoid and/or stop. In light of the other options with more data, it would seem sensible to substitute bempedoic acid for an alternative at the moment. The half-life for bempedoic acid is 19 hours at steady state in humans.

Bile acid sequestrants
This has historically been one of the only treatment options for LDL-cholesterol during pregnancy as bile acid sequestrants are not absorbed systemically and do not cross the placenta [14]. Bile acid sequestrants can reduce the absorption of fat-soluble vitamins and folic acid, therefore supplementation is recommended, and they only reduce LDL by 15%. Colesevalam is better tolerated than cholestyramine (less constipating).

Lipid apheresis
This is a safe option for either high cholesterol or triglycerides but difficult to access and not widely available. Guys & St Thomas (GSTT) and Southampton are locations that have this service.

Aspirin
It should be continued (75 – 150 mg OD) if previously prescribed and otherwise commenced for pre-eclampsia prevention at a dose of 150 mg per day from 12 weeks' gestation.

- **<u>Triglyceride reducing medicines.</u>**

Fibrates (fenofibrate) and omega-3 fish oils (e.g OMACOR)
They have been used to treat hypertriglyceridaemia and are recognised therapeutic strategies, combined with a low-fat diet.

Icosapent ethyl (IPE)
A purified omega-3 has been used for hypertriglyceridemia in the US for over a decade (but only more recently been granted a secondary prevention licence in this country). Thousands of pregnant women (>11,000) have been treated with omega-3 during pregnancy in trials [15]. However, these generic drugs are a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ethyl esters. EPA and DHA are biochemically and clinically distinct [16]. Therefore, the safety and toxicity of mixed EPA+DHA compared to pure EPA may differ, and their role in pregnancy is unclear.

There are case reports of IPE usage in pregnancy, primarily for treatment of hypertriglyceridaemia and pancreatitis risk. In all cases no adverse outcomes were reported, and the women avoided pancreatitis [17-21]. There may be limitations on use, due to the UK licence, however it would seem that IPE may be an option for pancreatitis prevention, CVD risk reduction, and treatment of hypertriglyceridaemia in pregnancy.

2.4 Breast/Infant feeding

For most postnatal women and people, treatment with bile acid sequestrants is safe, the risk-benefit of other lipid lowering therapies must be discussed with the mother.

Bile acid sequestrants are safe but there are no clinical trials examining the safety of other lipid lowering therapies in breastfeeding. The hydrophilic statins rosuvastatin and pravastatin may be associated with lower transfer into breast milk than other statins [22, 23]. Atorvastatin can also be considered during breastfeeding[24]. Ezetimibe and PCSK9i have data and licences for paediatric populations but the inclisiran paediatric trial is awaited and there are no data for bempedoic acid [25]. This does not necessarily mean that presence in breast milk of lipid lowering therapy has no risk for the infant, but reassuring when one is discussing the risks and benefits in high-risk women.

2.5 Summary

There is a need to be more proactive at maintaining good lipid control during pregnancy for both mother and child. We would always recommend seeking support and advice from maternal medicine and lipidology services as appropriate.

Table 2: Summary recommendations on use of lipid lowering therapies in Pregnancy.

Drug	Recommendations (all shared decisions)
Statins	Do not stop automatically in high-risk patients. Consider cessation in first trimester and then restart in second trimester or continue throughout (based on preference and risk).
Ezetimibe	Do not stop automatically. Lack of data however, so consider cessation and substitute e.g. bile acid sequestrants (base on preference and risk)
Bile acid sequestrants	Safe during conception, pregnancy and breast feeding. Caution with risk of vitamin deficiencies
Bempedoic acid	Stop during conception, pregnancy and breast feeding
PCSK9i	Continue if on evolocumab or alirocumab, consider starting in those stopping other therapies if eligible
Inclisiran	Do not continue during pregnancy. If eligible consider administration prior to conception
Icsosapent ethyl	Continue if on it, consider starting in those eligible. Consider for hypertriglyceridaemia (outside current UK licence)
Fibrates e.g. fenofibrate	Treatment for hypertriglyceridaemia in pregnancy, particularly in those with previous pancreatitis in pregnancy due to hypertriglyceridaemia or with known genetic or secondary issues causing pre-existing hypertriglyceridaemia (consider if triglycerides >5 mmol/L prior to conception, or >10 mmol/L during pregnancy).
Omega 3 fish oils e.g. OMACOR	Treatment for hypertriglyceridaemia in pregnancy, particularly in those with previous pancreatitis in pregnancy due to hypertriglyceridaemia or with known genetic or secondary issues causing pre-existing hypertriglyceridaemia. Consider if triglycerides >10 mmol/L but note safety notice secondary to atrial fibrillation so consider dietary input, glycaemic control and fibrates in preference. High doses up to 4 g twice daily may be required (unlicensed use – specialist recommendation only)

3. Research Recommendations

This guideline has been developed in the absence of national guidance and has been developed with local subject experts and liaison with medical staff from pharmaceutical companies.

Research is required on the safety of lipid lowering therapies throughout pregnancy to both the baby and woman but particularly on the effects to the mother of stopping therapy. Nothing is known about whether the child's cardiovascular outcome and lipid concentrations can be improved by treating the mother. Best regime, time to start, use of injectable agents prior to conception have not been studied.

4. Related guidelines, policies and pathways

NICE NG238, CG71, MHRA (use of medicines in pregnancy and breast feeding).

5. Monitoring the effectiveness of this guideline

Issue being monitored	**Monitoring method**	**Responsibility**	**Frequency**	**Reviewed by and actions arising followed up by**
Automatic cessation of lipid lowering therapy, or not offering treatment in the first place, due to chance of patient becoming pregnant/being pregnant	Number of women on lipid lowering therapy during pregnancy	Kate Shipman, pathology	Triannual	Collegiate review by lipid specialists, maternal medicine specialists and cardiovascular disease leads.

Appendix 1: Guideline Version Control Log

This should be included for all new and updated guidelines, summarising the changes between the current and previous version.

Do not list minor and stylistic changes or changes which do not alter the processes described.

If the update includes a significant reorganisation of the material, indicate this and list the main areas where the process itself has changed.

Change Log – Guideline Name		
Substantive changes since previous version/ development of new guideline	**Reason for Change/ development of new guideline**	**Version Control**
N/A first version	**First version**	**Version 1 2024**

Appendix 2: Due Regard Assessment Tool

To be completed and attached to any guideline when submitted to the appropriate committee for consideration and approval.

		Yes/No	Comments
1.	Does the document/guidance affect one group less or more favourably than another on the basis of:		
	Age	*yes*	*Childbearing ages*
	· Disability	*No*	
	· Gender (Sex)	*yes*	*Women*
	· Gender Identity	*yes*	*Able to get pregnant therefore may include some individuals identifying as male*
	· Marriage and civil partnership	*No*	
	· Pregnancy and maternity	*Yes*	
	· Race (ethnicity, nationality, colour)	*No*	
	· Religion or Belief	*No*	
	· Sexual orientation, including lesbian, gay and bisexual people	*No*	
2.	Is there any evidence that some groups are affected differently and what is/are the evidence source(s)?	*yes*	*This focuses on a very specific group*
3.	If you have identified potential discrimination, are there any exceptions valid, legal and/or justifiable?	*no*	*Aim to stop discrimination against this group*
4.	Is the impact of the document likely to be negative?	*No*	
5.	If so, can the impact be avoided?	*n/a*	
6.	What alternative is there to achieving the intent of the document without the impact?	*n/a*	
7.	Can we reduce the impact by taking different action and, if not, what, if any, are the reasons why the guideline should continue in its current form?	*n/a*	
8.	Has the document been assessed to ensure service users, staff and other stakeholders are treated in line with Human Rights FREDA principles (fairness, respect, equality, dignity and autonomy)?	*yes*	

If you have identified a potential discriminatory impact of this guideline, please refer it to [Insert Name], together with any suggestions as to the action required to avoid/reduce this impact. For advice in respect of answering the above questions, please contact uhsussex.equality@nhs.net 01273 664685).

Appendix 3: Template Dissemination, Implementation and Access Plan

To be completed and attached to any guideline when submitted to Clinical Documents Approval Group for consideration and CDAG approval.

	Dissemination Plan	**Comments**
1.	Identify:	
	Which members of staff or staff groups will be affected by this guideline?	Any clinician looking after anyone who is considering becoming or is pregnant
	How will you confirm that they have received the guideline and understood its implications?	Ratified by Sussex APC so available to all GPs, maternal medicine services co-authored as did all lipidologists therefore all services who would be providing advice are aware. By taking through Trust process then hospital users can also use document
	How have you linked the dissemination of the guideline with induction training, continuous professional development, and clinical supervision as appropriate?	Included in lipid teaching but no routine training as this cohort it rare and usually discussed with maternal medicine or lipid clinic
2.	How and where will staff access the document (at operational level)?	Aim to get to SharePoint for Trust staff and on ICB website for community

		Yes/No	Comments
3.	Have you made any plans to remove old versions of the guideline or related documents from circulation?	n/a	
4.	Have you ensured staff are aware the document is logged on the organisation's register?	no	Will let internal specialists know when available

Appendix 4: Additional guidance and information

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