DYSLIPIDEMIA MANAGEMENT IN PREGNANT PATIENTS: A 2024 UPDATE

- Over several decades, the approach to treating dyslipidaemias during pregnancy remains essentially unchanged. The lack of advancement in this fieldis mostly related to the fact that we **lack clinical trials of pregnant patients** both with available as well as new therapies.
- While there are numerous novel therapies developed for non-pregnant patients, there are still many limitations in dyslipidaemia treatment during pregnancy.
- Besides pharmacotherapy and careful clinical assessment, the initiation of **behavioural modifications** as well as pre-conception management is very important.

INTRODUCTION

- The increase of lipid and lipoprotein levels during pregnancy is important for the proper growth and development of the foetus.
- During the first trimester, **lipids accumulate in the mother's body** to support foetal development, with this process starting around **the 7th week** of pregnancy and peaking by **the end of the second trimester.**
- In late pregnancy, stored lipids serve as a reservoir for fatty acid synthesis in placental tissue.
- The most significant lipid changes occur **during the second and third trimesters**.
- Total **cholesterol (TC) and triglyceride (TG) levels rise**, driven by increased lactogen, oestrogen, and progesterone.
- Triglycerides undergo the most significant increase, reaching two to four times their pre-

- Studies indicate **adecrease in LDL particle size (sdLDL)** which is considered particularly atherogenic.
- mitigated by **elevated levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (Apo A-I), which peak during the second trimester** and may offer potential protection against atherogenic lipid fractions.
- HDL-C functionality during pregnancy also depends on various factors,

  systemic inflammatory tone,
  Obesity
  diabetes,
  chronic kidney disease,
  and hypertension.

- **all pregnant women experience a natural increase in lipid levels**
- including those with pre-existing dyslipidaemia . The additional rise is particularly significant for this group, as discontinuation of lipid-lowering therapy during pregnancy leads to a gradual elevation in LDL-C levels,
- **resulting in increased exposure of the arterial vasculature to cholesterol over time**.
- While ~80% of dyslipidaemias are influenced by factors such as diet and lifestyle choices,
- **women with a genetic predisposition to dyslipidaemias may face heightened cardiovascular risks.**

- comparing plasma lipid concentrations between women **with and without FH** revealed that the relative **increase in lipid fractions** was **similar**.
- In the FH group, TC and LDL-C increased by28.7% and 29.6%
- in healthy pregnant women, it was 25.4% and 34.2%,
- Triglycerides showed an even greater increase, reaching 116% in the FH group, compared to 103.4% in healthy patients ($P < 0.05$).
- HDL did not exhibit significant differences between the two groups ($P < 0.05$).
- **Lipid levels returned to normal 3–6 months post-partum.**

- despite significantly higher baseline lipid levels, **no significant differences** in terms of
  - preterm births,
  - hypertension prevalence,
  - gestational duration,
  - body weight,
  - body length,
  - and head circumference

between patients with FH and those without FH before pregnancy.

- **elevated lipid values during pregnancy are considered physiological**, some evidence suggests potential associations with **adverse events**, such as

  pregnancy-induced hypertension, pre-eclampsia,

  gestational diabetes mellitus (GDM), preterm delivery, and macrosomia.

- **After delivery** post-partum impaired glucose tolerance post-partum dyslipidaemia in mothers.
- Napoli *et al.*30 reported a link between maternal hypercholesterolaemia and **early atherosclerosis development in children,**
- **foetal aortic lesions, rendering children susceptible to fatty-streak formation and atherosclerosis development**

- Lp(a) levels show a **significant increase during pregnancy in all women**.
- nearly **double** between **the 10th and 35th weeks** of pregnancy.
- Women with initially elevated Lp(a) levels will undergo a similar increase,
- Lp(a) is an **inflammatory lipoprotein** that could induce **endothelial dysfunction** in the systemic vasculature, including those in the placenta.
- This could compromise **placental arterial function**, potentially resulting in **high blood pressure in the mother and posing risks to**

- Elevated Lp(a) values are **observed in as many as 20–30% of pregnant women**, which can impact prognosis, **increasing the risk of pre-eclampsia, preterm delivery, or low birth weight.**
- promote **endothelial dysfunction**, possibly potentiating the development of pre-eclampsia.
- its **antifibrinolytic properties**, contributes to a **prothrombotic state**, which contributes to low birth weight and preterm labour.
- may also play a role **in reducing bleeding** during childbirth.
- recent guidelines from six Polish scientific societies recommend the measurement of Lp(a) for all pregnant women (IIb C).

- Another critical concern during pregnancy is **severe hypertriglyceridaemia**, which can be a life-threatening condition for both the mother and child.
- With triglycerides steadily increasing during **each trimester**,
- high risk of severe disturbances in **pre-pregnancy elevated triglyceride levels ≥ 500 mg/dL** (5.6 mmol/L), which can lead **to acute pancreatitis**, posing risks to both the foetus and mother

PRE-CONCEPTION MANAGEMENT AND LIPID SCREENING DURING PREGNANCY

- Before considering pregnancy in all patients with **previously diagnosed dyslipidaemia**, pre-conception referral to a cardiologist, clinical dietitian, and geneticist is recommended
- lipid disturbances were not included in the modified World Health Organization (mWHO) classification,
- **careful evaluation of potential pros and cons of the discontinuation of lipid-lowering treatment**.
- careful assessment of **maternal cardiovascular risk** should be performed together with the measurement of **lipid levels and Lp(a)**.
- The monitoring of lipid parameters should be further continued during the

- **The timing of lipid screening** during pregnancy is also not established
- **lipid testing to the routine prenatal check-up may lead to the improvement of a dyslipidaemia diagnosis**.
- Golwala *et al* . assessed 445 pregnant women among whom 236 (66%) performed lipid testing showing abnormal results in 25% patients (*n* = 59)
- **identified one woman with FH**.
- that this constitutes 0.4% of all tested women **repercussions for both the mother and the child**.

BEHAVIOURAL INTERVENTIONS

- Before contemplating the initiation of pharmacological interventions,
- arises from **the stark realization that a mere 0.1% of pregnant** women adhere to an optimal dietary regimen.
- there exist no tailored dietary directives for pregnant women with lipid disorders.
- Nevertheless, the choice of an appropriate dietary regimen should parallel that recommended for the average dyslipidemic patient, all while duly acknowledging the constraints imposed by pregnancy.
- Intervention based on the Mediterranean diet (**MedDiet**) was proved to **reduce the frequency of metabolic disorders post-pregnancy.**

- In a study by Melero *et al.*, **dietary modification** was implemented **before the 12th** week of pregnancy, and patients were observed **at two endpoints** post-delivery**:** at **3 months** and **3 years.**
- women who were randomized to diet including **extra virgin olive oil > 40 mL per day and nuts** (MedDiet) presented with

  better glycaemic and **lipid profiles**

  lower body mass index.
- A considerable portion of the guidelines pertaining to a healthful gestational diet mirror those of a dyslipidemic dietary approach.

- **should avoid overly restrictive diets**, and those with severe dyslipidaemia should consult a clinical dietitian.
- Alcohol and tobacco use are strictly contraindicated during pregnancy.
- Regular exercise and lifestyle adjustments enhance treatment efficacy.
- In recent years, numerous RCTs have addressed physical activity during pregnancy.
- In conclusion, it is imperative to institute both lifestyle interventions and concomitantly scrutinize gynaecological and cardiovascular outcomes.

PHARMACOTHERAPY

- Despite the **established association between dyslipidaemia during pregnancy and adverse events**, recent European Society of Cardiology (ESC) guidelines on cardiovascular diseases management during pregnancy have largely overlooked this topic. provide only limited information, primarily in a **short paragraph about statin therapy.**
- Similarly**, no recommendations are available from the Centers for Disease Control and Prevention (CDC).**
- The ESC guidelines on cardiovascular disease prevention in clinical practice advise **against the use of statins** in women of fertile age considering pregnancy.
- Moreover, due to limited data, treatment options for these conditions remain relatively scarce
- The limited stems from the common practice of excluding pregnant women from clinical

BILE ACID SEQUESTRANTS

- **only** bile acid sequestrants (BAS), such as cholestyramine, colestipol, and colesevelam, have received **approval**
- **is linked to the mechanism of action** of these drugs. BAS function by disrupting the enterohepatic circulation of bile acids, binding them in the intestinal lumen, and leading to their excretion in stool.
- fewer bile acids return to the liver, which activates hepatic bile acid production, a reaction that **consumes cholesterol**.
- increased hepatic cholesterol biosynthesis and an increase in LDL receptor expression on the surface of hepatocytes.
- BAS are known **to lower total cholesterol** levels and have a modest impact on ***reducing LDL-C levels.***

- The effectiveness of BAS is dosage-dependent.

monotherapy, these resins reduce LDL-C by ~20–30%,

combined with statins, they contribute an additional reduction of ~10%.

- their effect on triglycerides is limited and may even lead to triglyceride and VLDL elevation,

contraindicated in hypertriglyceridaemia (>400 mg/dL).

- It is essential to use BAS **alongside dietary modifications**.
- **reducing the progression of atherosclerosis**, which is associated with the decrease in LDL-C levels.
- The **maximum effect** of BAS is typically observed **after one month of therapy**,
- after discontinuation, LDL levels return to baseline values in approximately one

- the safest lipid-lowering drugs for use in pregnant women.
- **their adherence remains suboptimal** due to

  constipation, abdominal pain, loss of appetite,

  indigestion, bloating, vomiting, and heartburn,
- can impede the **absorption of fat-soluble vitamins, such as vitamin K**, potentially increasing the risk of neonatal cerebral bleeding, necessitating appropriate supplementation
- **to prevent reduced absorption of other medications**, ion exchange resins should be taken either 4 h before or 1 h after other medications.
- Based on available data, colesevelam (Cholestagel) appears to be the best-tolerated resin.

OMEGA-3 FATTY ACIDS

- Another viable treatment option during pregnancy
- **reduce triglyceride levels by 20–30%** and result in a slight decrease in non-HDL-C and apolipoprotein B levels.
- is dose-dependent and influenced by baseline lipid values.
- With **larger doses**, even up to 4 g/day , they have the potential to reduce the risk of **cardiovascular events**, as demonstrated in significant trials such as the Japan EPA lipid intervention study (JELIS),
- particularly the **Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (**REDUCE-IT) and its numerous sub-analyses.
- However, these findings are not specifically related to lipid lowering during pregnancy, as there are no data for this state.

- Beyond their triglyceride-lowering effects, the use of omega-3 fatty acids during pregnancy reduce the risk of

  preterm birth (<37 weeks),

  early preterm birth (<34 weeks),

  perinatal death,

  and low birth weight babies.

- it is important to note that omega-3 fatty acids may slightly increase the risk of

  large-for-gestational age babies

  their use may elevate the risk of atrial fibrillation.

IN SUMMARY

- effective option for patients with **severe hypertriglyceridaemia**,
- especially those at risk of pancreatitis (e.g. individuals with **very high levels > 500 mg**/dL who are **symptomatic** or have a **history of pancreatitis**),
- even when used in combination with fenofibrate, provided the benefits outweigh the risks

STATINS

- HMG-CoA reductase inhibitors, which are commonly used in the treatment of dyslipidaemia, have demonstrated substantial benefits in preventing cardiovascular events.
- is not recommended due to a lack of safety data, the potential **decrease in cholesterol synthesis and other lipid-derived substances in newborns**, and **most of all concerns of teratogenicity**.
- recommendation primarily relies on animal studies, which have exhibited findings such as **gastroschisis** and **skeletal malformations** in rats, **reduced birth weigh**t in rabbits and rats, and a **single human case involving a child with multiple inborn malformations.**
- Some human studies also suggested potential adverse birth outcomes

- Edison *et al*. reported a series of 20cases involving malformations in infants exposed to statins during the first trimester, including **limb deficiencies** (five cases) and **central nervous system defects (**five cases).
- in infants whose mothers were exposed to **lipophilic statins(**atorvastatin,simvastatin,lovastatin…)
- while no adverse birth outcomes were reported for infants whose mothers used hydrophilic statins(such as pravastatin,rosuvastatin)

- An analysis by Bateman *et al*. did not show significant teratogenic complications in agroup of 1152 women using statins in the first trimester of pregnancy
- In initial unadjusted analyses, the incidence of malformations in offspring from women who used statins during the first trimester was 6.34%, compared to 3.55% in offspring of non-statin users.
- adjusting for confounding factors, particularly pre-existing diabetes, nullified this heightened risk.
- **there were no statistically significant increases observed in any specific organ malformations** upon adjustment for confounders.

- A recently published meta-analysis of one case–control study and five cohort studies revealed no statistically significant elevations in the **incidence of major congenital anomalies** when comparing the statin exposed cohort to the control group
- However, an increase in the **risk of cardiac anomalies** was observed in individuals exposed to statins when unadjusted ORs were aggregated Upon further examination using adjusted ORs, there was no significant rise in the risk of cardiac anomalies among the statin-exposed cohort compared to the controls
- A significantly **diminished rate of live births** and an **elevated incidence of spontaneous abortions** were noted in the statin-exposed cohort.
- However, these observations may be linked with other unadjusted issues and

- The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) **reported the results of a real-world pharmacovigilance study**, showing that pregnancy-related statin adverse events were present **in 477 patients**.

lovastatin was linked with a higher risk of **foetal complications** and

pravastatin with a higher risk of **preterm birth** and **low birth weight**

- **pleiotropic effects**, have shown potential in **improving placental vascular remodelling**.
- **Pre-eclampsia,** a complication of pregnancy associated with maternal vascular inflammation, **may be mitigated by statin therapy, reducing the risk of its development**.
- the recent multicentre, double-blind, placebo-controlled STATIN trial with pravastatin did not demonstrate an impact on the incidence of pre-eclampsia.
- **No significant differences** were observed between the pravastatin group (548 patients) and the placebo group (543 patients) in terms of **pre-eclampsia** (14.6% vs. 13.6%), **gestational hypertension**,

- Despite potentially positive results, current guidelines generally advise discontinuing statin therapy in most pregnant patients.
- a recent statement from the FDA **removed the strongest warning against statins** and suggested that for **patients at very high risk of cardiovascular events**, the decision about treatment should be individualized.
- most suitable group of pregnant women with dyslipidaemia for statin treatment appears to be those with FH.

- Botha *et al*. retrospectively analysed **data from 39 pregnancies in females with homozygous FH** (HoFH).
- Among them, 19 patients were treated with statins before or during pregnancy.
- no statistically significant differences in pregnancy complications between HoFH and healthy patients.
- In this FH patient group, 84% of all pregnancies reached full term. The **rates of miscarriages and premature deliveries were both 8%** .
- Theauthors concluded that statin therapy appears to be safe for both the mother and child, offering a valuable therapeutic option for severe hypercholesterolemic patients, including those with HoFH.

- A systematic review and meta-analysis conducted by Vahedian-Azimi *et al.* included **23 studies** with **1 276 973 participants**.
- did not provide a clear association between statin therapy and an increased rate of **birth defects**.
- no significant links observed in separate analyses for **cardiac anomalies** and **other congenital anomalies**
- Another systematic review and meta-analysis by the same research group, comprising nine studies, assessed the effect of statins on the **incidence of stillbirth** (including 2350 participants), **foetal abortion** (8422 participants), and **preterm delivery** (483 participants).
- The results of the meta-analysis showed a correlation between statin use and the rate of spontaneous abortion

- appears that statin therapy may be a therapeutic option for patients with

  severe hypercholesterolaemia, especially those with **severe FH** and those at **very high or extremely high cardiovascular disease risk**

  history of acute coronary syndromes or strokes.

FIBRATES

- **Alternative options** for managing dyslipidaemia during pregnancy typically lack official approval.
- inadequate human data supporting the use of fibrates, and nicotinic acid has been reported in only a limited number of case studies.
- As a result these drugs are **not recommended** for use during pregnancy,
- ESC guidelines for 2018 explicitly stating that should only be considered when the **benefits clearly outweigh the risks**.
- Animal studies involving fenofibrate have shown various complications,

delayed delivery
reduced birth weight,
Increased post-implantation loss
skeletal and visceral abnormalities,
abortions
and foetal deaths.

- The AHA Scientific Statement **for Cardiovascular Considerations** in Caring for Pregnant Patients proposes the consideration of **fenofibrate or gemfibrozil** in the **second trimester** if **triglycerides are >500 mg/dL** despite lifestyle modifications.
- The AHA/American College of Obstetricians and Gynecologists (ACOG) Presidential Advisory states that **pregnant patients with a history of pancreatitis** may benefit from the use of fenofibrate **when** **triglyceride levels are >1000 mg**/dL.
- The use of fibrates during the **second trimester is after embryogenesis** occurs reducing the risk.
- **Studies in animals have found no increased risk of congenital malformations.**

EZETIMIBE

- **Insufficient data are available** regarding the use of ezetimibe, although it is considered a safe drug.
- Animal studies, in which ezetimibe was administered either alone or in combination with statins,

  demonstrated a higher incidence of **skeletal changes** in rats and **extra ribs** in rabbit thoraxes,

  with **no confirmed lethal embryo effects** in available animal studies.
- its use is limited to individual cases which the **potential benefits clearly** outweigh the risks.
- lipid-lowering **capacity of these drugs may be insufficient** to treatment goals for severe hypercholesterolaemia during pregnancy, **even when used in conjunction**

OTHER LIPID-LOWERING MEDICATIONS

- Limited or single studies have been conducted to assess
- proprotein convertase subtilisin:kexin type 9 (PCSK9) inhibitors (evolocumab, alirocumab), bempedoic acid, lomitapide, and inclisiran during pregnancy.
- In the case of evolocumab, studies showed a reduction in T cell-dependent responses following immunization with KLH in monkeys.
- a recently published case report documented **corpus callosum agenesis** in a child whose mother, diagnosed **with FH**, was using alirocumab, statins, and ezetimibe at maximum tolerated doses up to the 6th week of an unplanned pregnancy.
- However, two observational studies **on evolocumab** were prematurely terminated in December 2020, and a similar decision was made for the alirocumab registry during pregnancy (NCT03379558) in November 2020 .
- **Bempedoic acid**, due to the limited amount of data regarding its use during pregnancy, is contradicted.

- PCSK9 **plays fundamental roles in cellular differentiation and proliferation**.
- There is justifiable concern with respect to using agents that inhibit PCSK9 during **foetal development**.
- Ardissino *et al*. have introduced a highly innovative approach to assessing whether or not is plausible that PCSK9 inhibition might be harmful to the developing foetus by using genome-wide association studies including ~1.3 million patients.
- Using instrumental variants of PCSK9 that impact serum levels of LDL, these investigators showed that genetically proxied LDL-lowering through PCSK9 correlates with a higher odds of **malformations the skin** , and the **vertebral, anorectal, cardiovascular, tracheo-oesophageal, renal, and limbs .**

- Novel lipid-lowering drugs, including **volanesorsen** and **lomitapide**, have no available data during pregnancy, and are **therefore classified as 'C'—contraindicated** during pregnancy.
- **Volanesorsen** should be discontinued before attempting conception and
- **lomitapide** carries a risk of foetal toxicity.

- new and highly effective lipid-lowering drug, **inclisiran, an RNA silencing oligonucleotide**, requires administration only twice a year, has become available since 2021.
- Notably, data from the ORION-1 study have indicated that a single administration may be associated with a mean 41% reduction in LDL-C levels after 9 months.
- Despite its **unique safety profile** (with no apparent safety concerns compared to a placebo, apart from local side effects due to injection), **no data on its use in pregnant women** and their foetuses are available.
- it is purely hypothetical to consider employing inclisiran in high-risk patients **before and immediately after pregnancy, with the expectation of achieving ~40–50% LDL-C reduction.**

LIPOPROTEIN APHERESIS

- An **alternative therapeutic** option for hyperlipidaemia during pregnancy is lipoprotein apheresis (LA)
- **mechanical method designed to remove atherogenic lipoproteins** [LDL-C and Lp(a)] from plasma.
- filtering LDL, VLDL, Lp(a), alpha-2-macroglobulin, and coagulation factors, after which the plasma is returned to the bloodstream.
- This process has been shown to be safe for pregnant women

- The **primary clinical indication** for lipoprotein apheresis in pregnant patients is **HoFH**.
- high LDL-C levels and less-than-optimal responses to lipid-lowering therapy, should be offered bi-weekly LDL apheresis.
- Ogura *et al*. **reported 10 successful deliveries in seven patients with HoFH**, whereas two pregnant patients with **HoFH who did not receive lipid apheresis died** during pregnancy.
- lipoprotein apheresis has been employed in cases of severe hypertriglyceridaemia to prevent pancreatitis.
- Decisions regarding the use of lipoprotein apheresis should be made carefully, considering the potential benefits and risks associated with the procedure.

CONCLUSIONS

- Dyslipidaemia and the management of lipid and lipoprotein levels during pregnancy remain significant concerns, as they may lead to adverse outcomes for both the mother and the child.
- Current guidelines recommend discontinuing lipid-lowering treatment, except for BAS, one to two months before planned pregnancy or as soon as the pregnancy is detected, with no specific clinical guidance for severely hypercholesterolemic women, those with a high risk of cardiovascular disease, or those who have already experienced a cardiovascular event.
- a proportion of pregnancies remain unplanned and therefore lipid-lowering treatment may be continued after conception, leading to an increase in statin exposure during pregnancy.
- we observe an increase in the age at which women experience their first pregnancy,

- Pregnancy represents a period of heightened susceptibility to the progression of atherosclerosis. This vulnerability arises from the physiological increase in LDL-C, which is further exacerbated by the cessation of cholesterol-lowering treatment.
- On the other hand, there are data suggesting that temporary discontinuation of treatment has no adverse consequences.
- A retrospective review by Nangrahary *et al.* of 13 women with heterozygous FH (HeFH) proved good pregnancy outcome despite loss of statin treatment. the cessation of cholesterol-lowering therapy ranged between 12 months and 3.5 years

- the approved treatment methods are limited to behavioural interventions, including adopting a healthy lifestyle and diet, as well as the use of BAS, omega-3 fatty acids, and LDL apheresis.
- **Fenofibrate and ezetimibe might be considered in some cases**, but only when the potential benefits clearly outweigh the risks.
- the current guidance of the International Atherosclerosis Society, which recommend that **statins and other cholesterol-lowering drugs be discontinued and that of bile acid sequestrants be initiated 3 months before a planned pregnancy**.

- In patients with **FH who become pregnant while taking statins, ezetimibe, PCSK9 inhibitors, or other lipid-modifying therapies should be discontinued**.
- Patients should be reassured that stopping these therapies is unlikely to harm the foetus.
- The guidance recommends a different approach for **women with HoFH and clinical atherosclerotic cardiovascular disease, when statin continuation** should be considered despite pregnancy.
- Other **lipid-modifying** therapies can be considered especially after **the first trimester** when the LDL-C goal is not achieved, and lipoprotein apheresis is not available or feasible to initiate
- the European Atherosclerosis Society (EAS) on HoFH management are similar.

- According to the 2023 update EAS Consensus Statement, women with HoFH should be offered weekly or fortnightly lipoprotein apheresis during pregnancy.
- If LA is unavailable, **the continuation of statin therapy should be considered** or
- reintroduction of **a statin plus other lipid-lowering** therapy from the **second trimester** onwards. Evidence suggests safety in this approach.
- The FDA has recognized the favourable risk/benefit ratio of statins in high-risk pregnant women, especially those with HoFH.

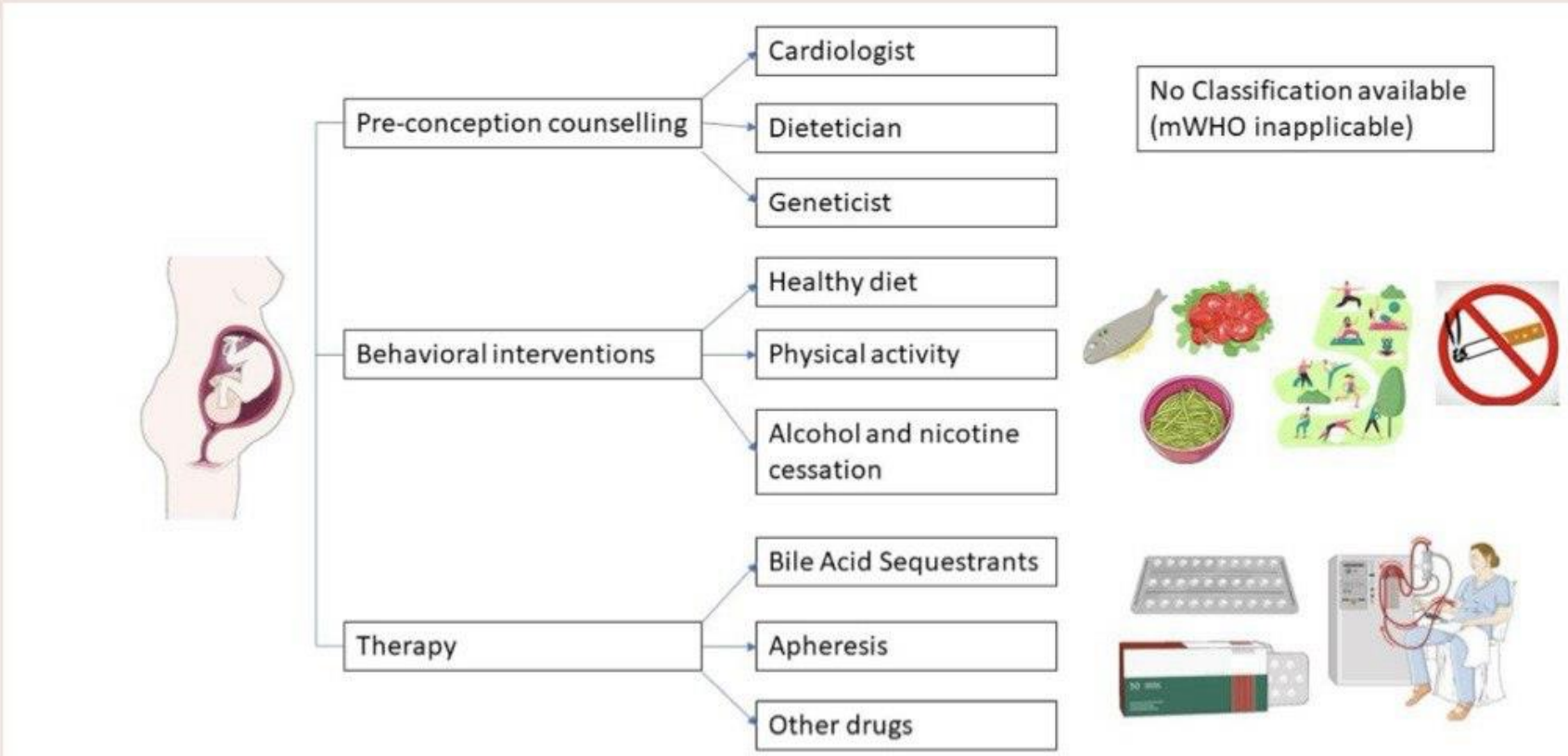

Figure 1 Lipid management approach during pregnancy (images from: Dall-e and smart.servier.com).


Thank you
For your attention