Università degli studi di Roma “Sapienza”
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# HYPERLIPIDEMIC PANCREATITIS IN PREGNANCY

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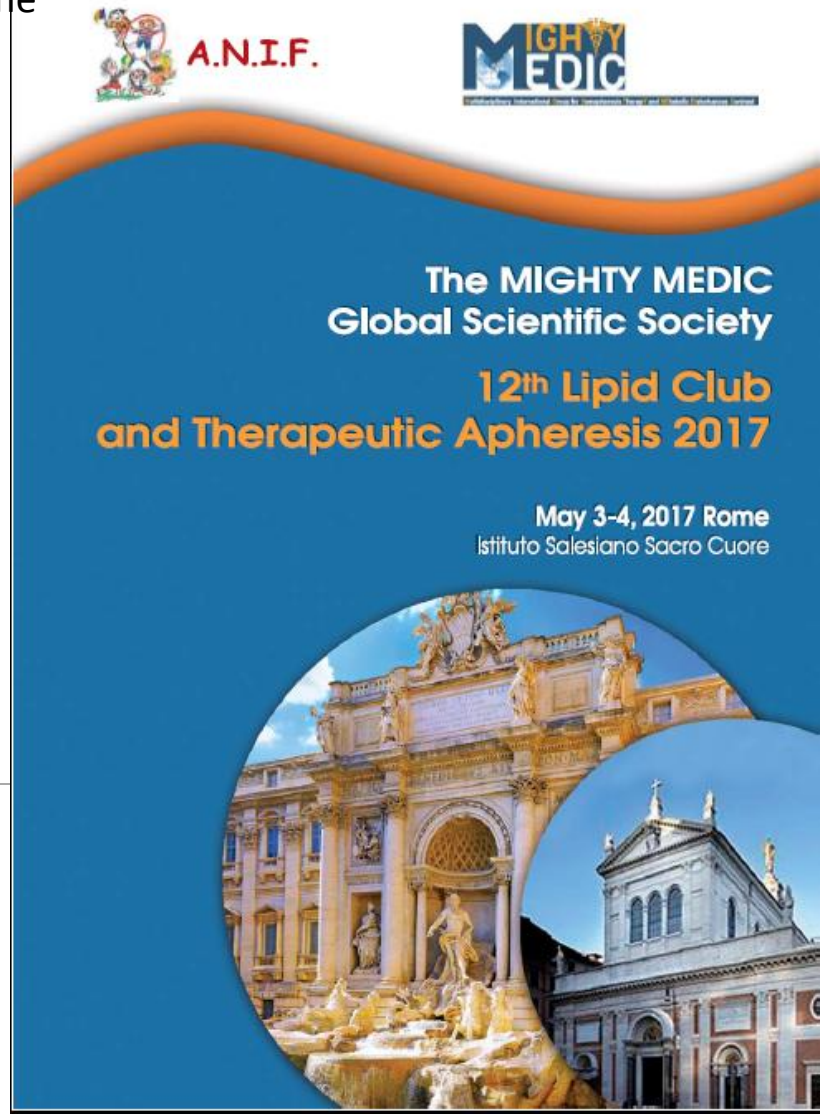
DOTT.SSA I. ZANNINI



# HOW LIPOPROTEIN METABOLISM CHANGES IN PREGNANCY

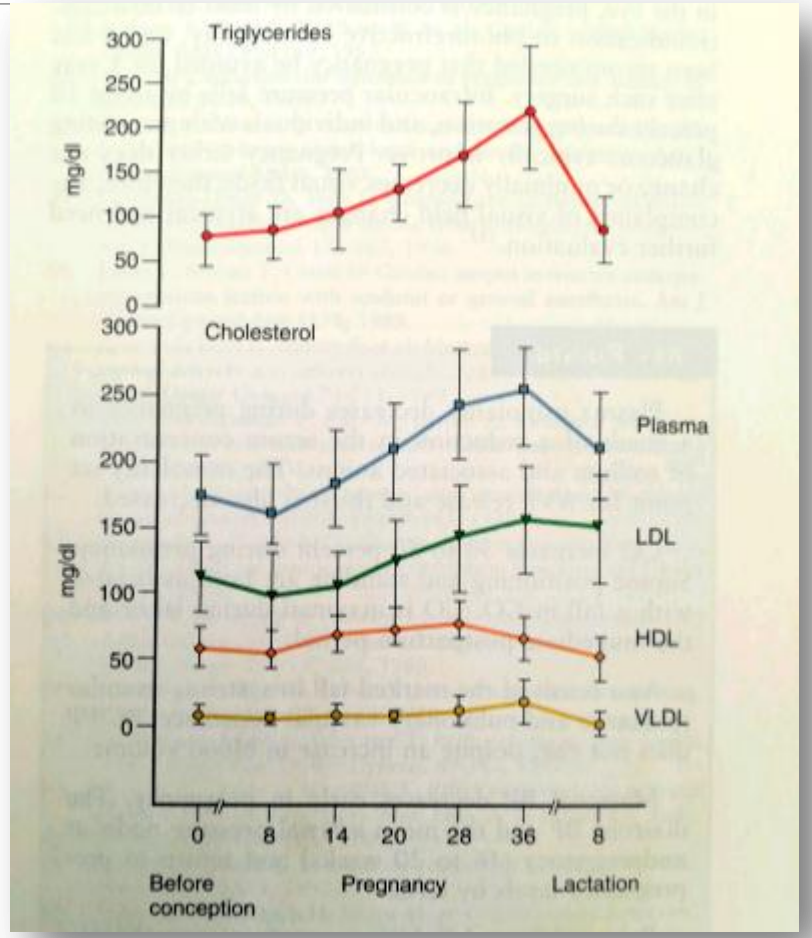
During pregnancy significant alterations of lipid homeostasis occur to ensure transfer of nutriens to the fetus

Cholesterol increases up to 20-40% both HDL than LDL

***Triglyceride (TG) levels increase from first trimester and are 2-3 fold in third trimester with an increase of both VLDL and chylomicrons***

***Further triglyceride increase is seen at all gestational stages in diabetic pregnancies***

Increased concentrations of triglycerides in IDL, LDL and HDL, suggesting triglyceride-enrichment of these circulating lipoproteins.




Alyse S. et Al, Severe Hypertriglyceridemia in Pregnancy. J Clin Endocrinol Metab, August 2012, 97(8):2589–2596

# WHY LIPOPROTEIN METABOLISM CHANGES IN PREGNANCY ?

| | | |
|---|---|---|
| **I/II trimester** | ↑ **Progesterone** | Incease appetite, weigth gain, fat stores |
| **II/III trimester** (increase fetal nutritional requireements) | ↑ **Estrogen**<br>↑ **Human Placental Lactogen** | Increase lipogenolisis and VLDL syntesis<br>Decrease hepatic lipase activity<br>Insuline resistence decreases LPL activity |

Alyse S. et Al, Severe Hypertriglyceridemia in Pregnancy. J Clin Endocrinol Metab, August 2012, 97(8):2589–2596

# FAT PLACENTAL TRANSPORT



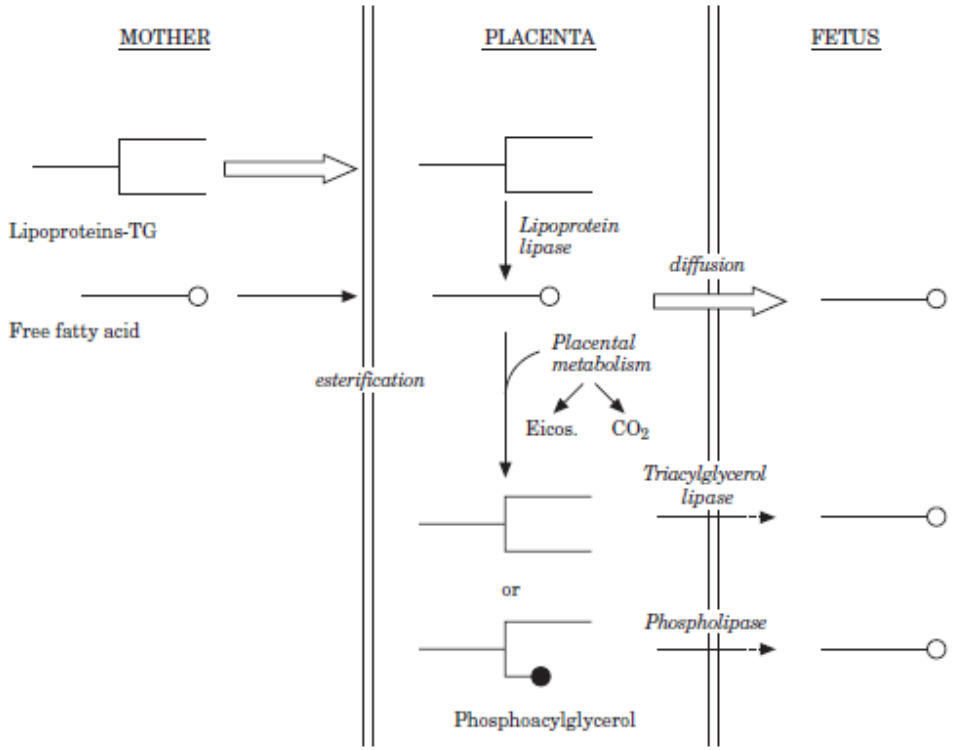



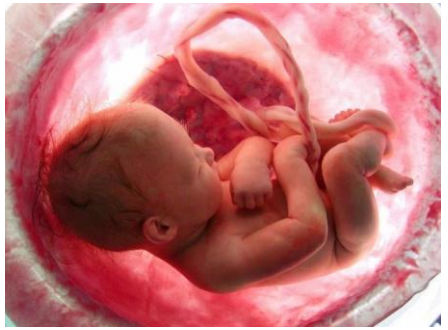

**Figure 4.** Schematic representation of the placental transfer of fatty acids to the fetus.

**Maternal serum TG don't cross the placenta** and free fatty acid (FFA) transfer is limited.

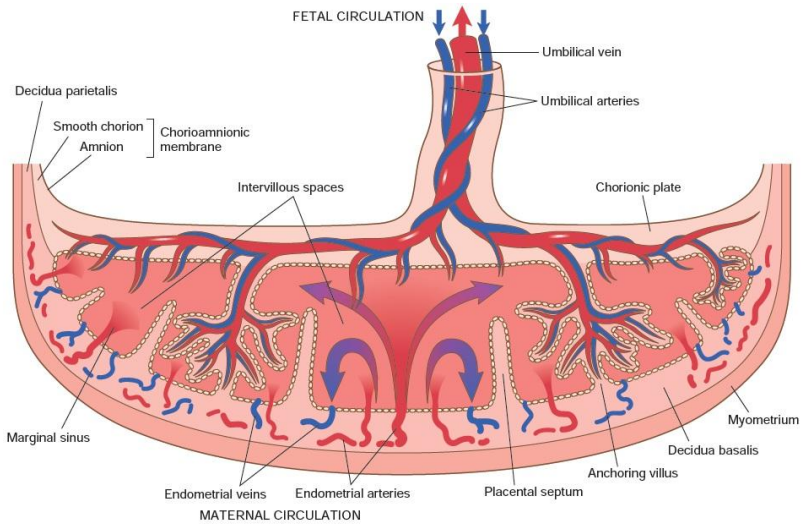
Maternal plasma TG are taken up and hydrolyzed by the placenta, that presents both lipoprotein receptor and lipoprotein lipase, and after releases to the fetus as free fatty acids and glycerol, that the fetal liver can esterify in TG


Herrera E., Implications of dietary fatty acids during pregnancy on placental, fetal and neonatal development- A review. Placenta 2002

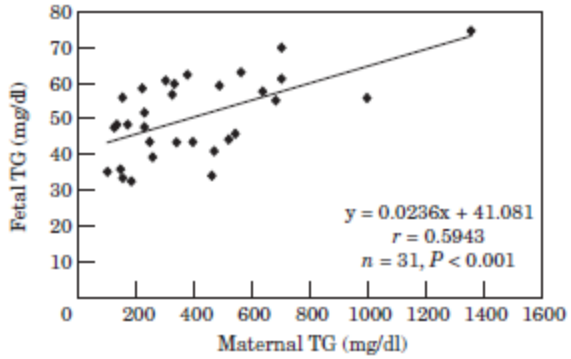
# FAT PLACENTAL TRANSPORT



TGs carry on essential fatty acid that are **fundamental** for fetal growth and have a key role in the brain development and visual function.




It was reported in several studies that **maternal serum TG levels** had a more important and independent effect on **fetal weight at term** than maternal plasma glucose in non diabetic women.




Herrera E., Implications of dietary fatty acids during pregnancy on placental, fetal and neonatal development- A review. Placenta 2002

# PREGNANCY IN HYPERTRIGLYCERIDEMIC (HTG) PATIENT

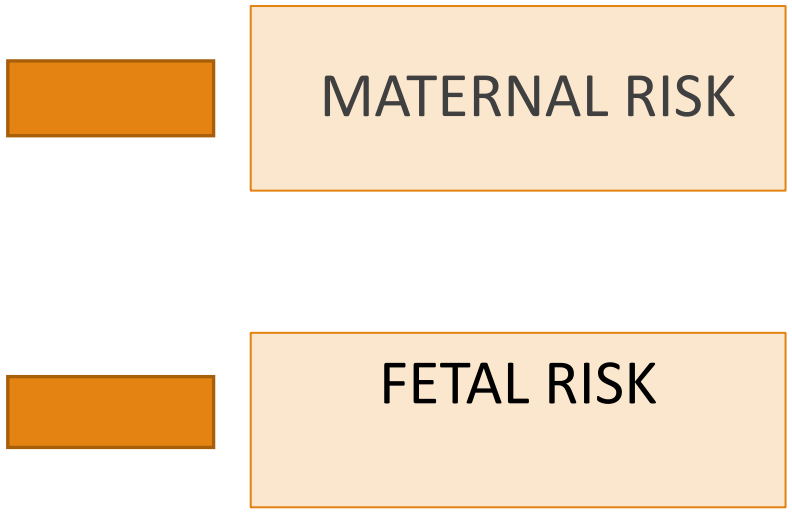
Severe HTG is defined as fasting plasma triglyceride level above 95° percentile for non pregnant population and tipically HTG occurs in presence of an underlying genetic abnormality in triglyceride metabolism

| **Genetic factors** | |
|---|---|
| Increased production | - Familiar combined hyperlipidemia<br>- Familiar hypertriglyceridemia |
| Reduced lipolysis | - Familiar chylomicronemia disorder<br>- Deficit LPL |
| **Secondary factors** | |
| Other disease | - Insuline resistence<br>- Hypotyroidism<br>- Nephrotic syndrome |
| Drugs/toxic | - Glucocorticoids<br>- Beta-blockers<br>- alcohol |

***Pregnant women with plasma TG greater than 1000 mg/dL, show an increased risk of acute pancreatitis***

Wong B et Al, Severe gestational hypertriglyceridemia: A practical approach for clinicians. Obstetric Medicine 2015, Vol. 8(4) 158–167

# PREGNANCY IN HYPERTRIGLYCERIDEMIC (HTG) PATIENT: COMPLICATIONS




**Direct harmful oxidative effect on the endothelium of placental vasculature and other vascular beds**

# PREGNANCY IN HYPERTRIGLYCERIDEMIC (HTG) PATIENT: MATERNAL RISK

| | |
|---|---|
| ACUTE PANCREATITIS | Approximately 1 in 1,000 to 3 in 10,000 births, more often in the second/ third trimester |
| HYPERVISCOSITY SYNDROME | Caused by excessive levels of chylomicrons |
| HYPERTENTIONS AND PRE-ECLAMPSIA | Hypertriglyceridaemia is associated with the onset of pre-eclampsia |
| CARDIOVASCULAR RISK | Seems to be limited |

Vrijkotte T.G.M. et Al, Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study. J Clin Endocrinol Metab, November 2012, 97(11):3917–392
Gallos ID: et Al, Pre-eclampsia is associated with, and preceded by, hypertriglyceridaemia: a meta-analysis. BJOG 2013

# PREGNANCY IN HYPERTRIGLYCERIDEMIC (HTG) PATIENT: FETAL RISK

| | |
|---|---|
| MACROSOMIA | Several studies found positive correlation between maternal TG and larger neonatal fat mass and higher birth weight |
| PRETERM BIRTH<br>Neonatal prematurity | Some studies found an association between high TG levels and PTB.<br>- Pre-eclampsia<br>- High maternal BMI |
| LOW BIRTH WEIGHT | Reduction of dietary intake |
| FETAL DEATH | Not confirmed |
| High CV risk of in adult life | Diabetes and hypertension |

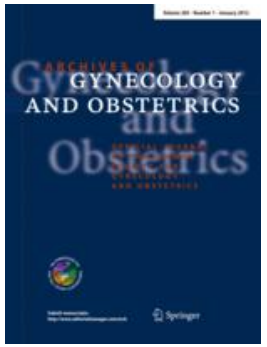
Vrijkotte T.G.M. et Al, Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study. J Clin Endocrinol Metab, November 2012, 97(11):3917–392

Arch Gynecol Obstet (2017) 295:313–323
DOI 10.1007/s00404-016-4216-5

MATERNAL-FETAL MEDICINE

# Maternal lipid profile and the relation with spontaneous preterm delivery: a systematic review

Maryam Moayeri[1] · Karst Y. Heida[1,2] · Arie Franx[1] · Wilko Spiering[3] · Monique W. M. de Laat[4] · Martijn A. Oudijk[1,4]




Tot-Chol level as an individual determinant for sPTD is clinically useless.

The analysed data on pre-pregnancy and pregnancy TG levels were highly heterogeneous. Yet, they showed a tendency towards no association between measured TG concentrations and the risk of sPTD.

Only two large cohort studies suggested that high TG levels are associated with increased risk of sPTD, but both studies did not adjust for pre-pregnancy BMI that is a well known risk factor for PTD

Arch Gynecol Obstet (2017) 295:313–323

# HYPERLIPIDEMIC PANCREATITIS IN PREGNANCY

**Acute hyperlipidemic pancreatitis** in pregnancy is uncommon (approximately 1 in 1,000 to 3 in 10,000 births) but often life threatening for the mother and fetus, is the second cause of pancreatitis in pregnancy after biliary tract disease.

75% of cases occurring in the second- third trimester and tends to be a more severe than pancreatitis due to gall stone disease

**Etiology**: pancreatic lipase hydrolyze TG with accumulation of fatty acids in the pancreas, resulting in oxidative damage to the vascular endothelium and the pancreatic acinar cells. Furthermore chylomicronemia-related hyperviscosity  may cause local ischemia and necrosis in the pancreas.

Padmavathi Mali. Pancreatitis in pregnancy: etiology, diagnosis, treatment, and outcomeHepatobiliary Pancreat Dis Int,  Vol 15,  No 4 • August 15,  2016.

# HYPERLIPIDEMIC PANCREATITIS IN PREGNANCY

Complications includes pseudocysts, pancreatic necrosis, significant electolyte alterations, adult respiratory distess syndrome, DIC, shock untill mother death.

**Early diagnosis and management in specialized neonatal intensive care units in the last few years lead to decrease maternal mortality to <1% from 37% and the perinatal mortality to 0–18% from 11–37%.**

Tang S.J. et Al. Acute pancreatitis during pregnancy. CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:85–9

# HYPERTRIGLYCERIDEMIA IN PREGNANCY: THERAPY

| | | |
|---|---|---|
| Low fat diet (<20% calories from fat) | Reduce Tg level | Patient adherence<br>Risk of fetal essential fatty acid deficiency (impared vision) |
| Omega -3 fatty acid<br>(3-4 gr die) | Reduced TG by 25-50%<br>Avoid fetal essential fatty acid deficienty | Safe in pregnancy |
| fibrates | Reduced TG in variable response, due to genotipe | No fetal damage was reportated in animal model and case reports |
| insuline | Can activate LPL in diabetic patients and reduce TG | No use in euglycemic patients, risk of hypoglycemia |
| Heparin iv | Liberate endothelial LPL and reduce TG | Hemorrhagic risk! |
| Statins | No significant TG lowering effect | Fetal safety uncertain |
| **Therapeutic apheresis** | **Rapid removal of TG-rich lipoprotein** | **High cost**<br>**Transient effect** |

Wong B et Al, Severe gestational hypertriglyceridemia: A practical approach for clinicians. Obstetric Medicine 2015, Vol. 8(4) 158–167
Alyse S. et Al, Severe Hypertriglyceridemia in Pregnancy. J Clin Endocrinol Metab, August 2012, 97(8):2589–2596

# HYPERTRIGLYCERIDEMIA IN PREGNANCY: THERAPEUTIC APHERESIS

In patients with markedly elevated triglycerides and severe pancreatitis total plasma exchange (TPE) may be used to rapidly remove chylomicrons and lower plasma triglyceride levels.

Some experiences suggest the use of TPE in the treatment of SHTG as prevention of pancreatitis.

The American Society of Apheresis (ASFA) indicated the Plasma Exchange (TPE) as category III ASFA (2013)
"Optimum role of apheresis therapy is not established. Decision making should be individualized" with Grade of Recommendation 2

***TPE reduces triglycerides by 60–70% in a single procedure resulting in a clinical and laboratory improvement of acute pancreatitis. TPE was confirmed as a safe method and did not have any adverse effect for neither the mother or fetus.***

# PREGNANCY IN HYPERTRIGLYCERIDEMIC (HTG) PATIENT: POST PARTUM AND BREASTFEEDING

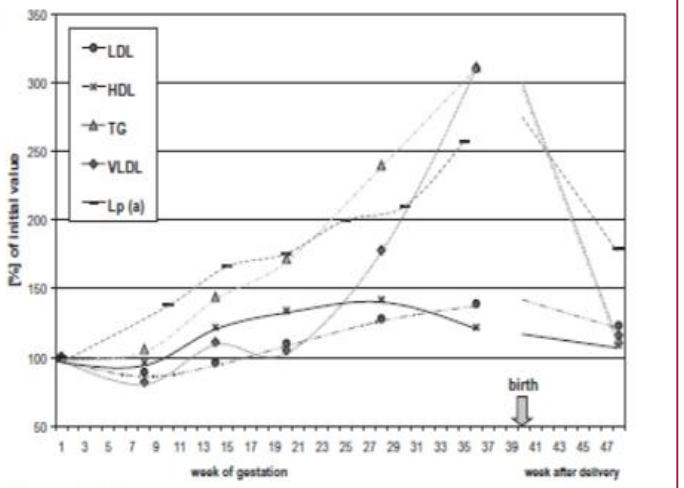



FIG. 2. Potential changes of the blood concentrations of low-density lipoprotein (LDL), high density lipoprotein (HDL), very low-density lipoprotein (VLDL) cholesterol, triglycerides (TG), and lipoprotein (a) (Lp(a)) during normal pregnancy [% of initial value] (modified from 18,19,21,22).

Delivery is estimated to lower triglycerides levels by 15-20% within 24 H returning to non pregnant level during the puerperium.

During breastfeeding we can use the same drugs:

1. Low fat diet;
2. Omega 3 supplementation;
3. Fibrates (that are secreted in maternal milk, with no reported cases of neonatal adverse effects)

# PREGNANCY IN HYPERTRIGLYCERIDEMIC (HTG) PATIENT: MANAGEMENT

Low fat low glycemic carbohydrate diet

Omega 3 to avoid essenzial fatty acid deficiency

moderate physical activity

Avoid secondary factors: alcohol, hyperglycemia, hypothyroidism, glucocorticoids

Consider fibrates after first trimester

If refractory consider hospital admission for supervised fasting and parental nutrition

Consider IV insulin if hyperglycemic

Consider therapeutic apheresis if severe HTG pancreatitis and to achieve proper gestational age for delivery

Rivised from : Wong B et Al, Severe gestational hypertriglyceridemia: A practical approach for clinicians. Obstetric Medicine 2015, Vol. 8(4) 158–167.

# CASE PRESENTATION

We present the case of a primigravida of 35 years old at **25 weeks of gestation**

***Familiar History:***

Father, 61 years old, hypertriglyderidemia and hypertension

***Medical History:***

Hypertriglyceridemia and hypercholesterolemia treated before pregnancy with omega-3 fatty acids.

Chronic hypertension

***Current Therapy:***

Alfametildopa 250 mgx3

C-ASA

Folic acid

# CASE PRESENTATION – at admission Day 1

The patient presented to the emergency room with severe addominal pain, nausea and vomiting.

Blood pressure was 140/85

In consideration of abdominal syntoms and blood pressure level was suspected a diagnosis of pre-eclampsia.

But

proteinuria was negative

and

Blood tests revealed a lipemic sample due to a very elevated **plasma triglycerides that was undetectable**, liver enzymes and amylase was normal. Cholesterol was 1489mg/dl, lipase undetectable.

Abdominal ultrasound reveled pancreatic inflammation with no signs to gallstones or biliary tract dilatation.

RMI : Pancreas size increase due to edema, two hypointense cysts due to necrosis

# CASE PRESENTATION – day 1

**A diagnosis of Hypertriglyceric pancreatitis was made**

Conservative treatment was started: controlled fasting, omeprazole, antibiotics (cephalosporins) and fluid rehydration.

Fetal heart monitoring and ultrasonund were performed : fetal weigth was appropiated for gestational age, amniotic fluid index was normal, no sign of fetal stress was detected.

# CASE PRESENTATION – day 2

**TG 4425 mg/dL; cholesterol 1184 mg/dL**; Amylase 86 U/L; lipase 180 U/l; calcemia 6.2; PCR 237000

First procedure of therapeutic apheresis was conducted – **Total Plasma Exchange** –

The volume of the plasma extracted (2000cc) was replaced with 5% albumin and heparinized saline.

Patient developed adult respiratory distress syndrome (ARDS) and was **moved to Intensive Care Unit** (tachycardia, tachypnea with hypoxemia and acidosis) where she started Noninvasive ventilation (NIV) and parental nutrition.

# CASE PRESENTATION: day 3 and 4

Second and third TPE procedures (reduction of TG value and clinical improvement).

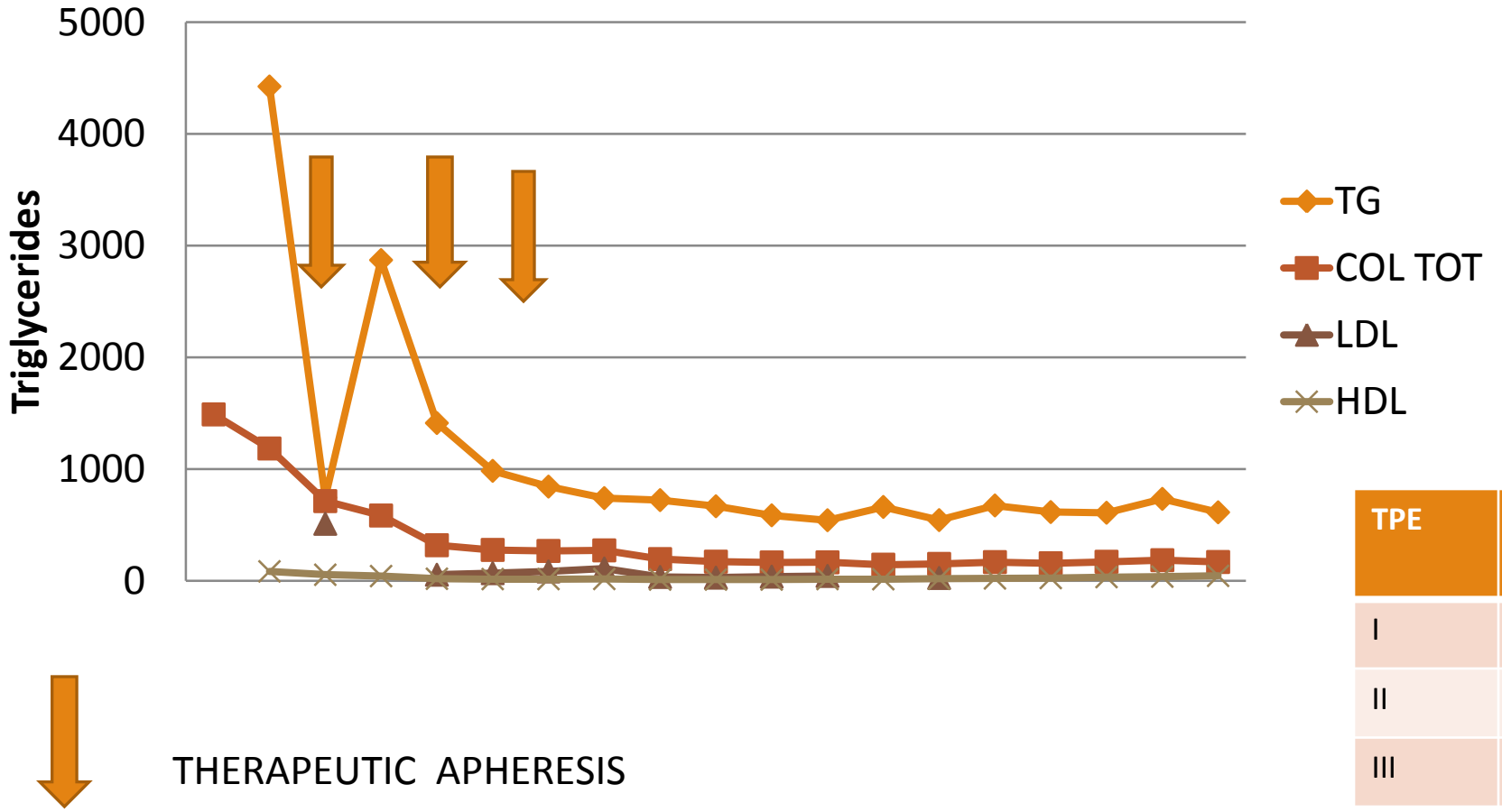
Days 4:

Fenofibrate 200 mg/day

Omega-3 fatty acids 4g/day

Omeprazole 40mg/day

# CASE PRESENTATION




| TPE | TG BEFORE-TPE | TG AFTER-TPE | DELTA % |
|---|---|---|---|
| I | 4425 | 744 | 83% |
| II | 2871 | 1412 | 50% |
| III | 984 | 667 | 32% |

# CASE PRESENTATION

She was discharged at 27 weeks' GA , asymptomatic,  TG level 629mg/dL

Therapy: fenofibrate 200mg once daily, omega3 fatty acids 3g once daily, and  low fat diet

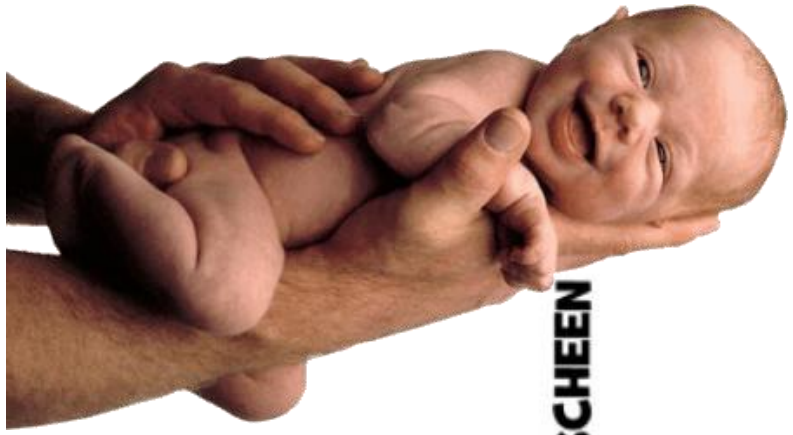
Fetal well-being was monitored with serial ultrasound which showed good fetal growth, normal amniotic fluid volume. The only abnormal finding was an increase of uterine artery  resistence in the maternal velocimetry while fetal velocimetry was normal.

37 weeks' GA : spontaneous labor, with an uncomplicated delivery of a healthy child, male, weight 2860gr, Apgar 8/9.

Analysis for genetic familiar dyslipidemia for this patient and her relatives are ongoing

# CONCLUSIONS

1. No clinical guidelines exist for hypertriglyceridemia in pregnancy
2. Pancreatitis clinical presentation can mimick other condition (pre-eclampsia; placental abruption…)
3. Therapy with fibrates and omega 3 fatty acid can be usefull from second/third trimester
4. Therapeutic Apheresis is safe for mother and fetus and can be used to overcome acute event and reach more advanced gestational age



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SHUKRIA
TINGKI
SUKSAMA
EKHMET
SPASIBO
DENKAUJA
NENACHALJHYA
WABEEJA
MAITEKA
YUSPAGARÀTAM
HUI
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HATUR
UNALCHÉESH
EKOJU
SIKOMO
MAKETAI
MINMONCHAR
MERABANI
MEHRBANI
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GAEJTHO
LAH
TAVTAPUCH
MEDAWAGSE
GOZAIMASHITA
EFCHARISTO
AGUYJE
FAKAAUE
BAIKA
AXAR
BOLZÏN
MERCI

Lipoprotein apheresis involves the physical removal of lipoproteins from the blood and is employed only in patients where lifestyle and pharmacologic treatment is not capable of decreasing lipoproteins to acceptable levels

plasmapheresis has been utilized to rapidly decrease plasma triglyceride levels in patients with very high triglyceride levels and pancreatitis.

The presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, phospholipase $A_2$, and intracellular lipase activities, allows the release to the fetus of polyunsaturated fatty acids transported as triglycerides in maternal plasma lipoproteins.

Maternal triglycerides don't freely cross the placenta but serve as important source of energy for the mother

| AUTORS | YEAR | WEEKS ON ONSET | TERAPY | DELIVERY | MOTHER | NEONATAL |
|---|---|---|---|---|---|---|
| Lim R. | 2015 | 23 | Insuline, fenofibrate, omega-3, TPE | 33 Recurrent pancreatitis and placental abruption | | GOOD |

**TABLE 3.** Management of elevated TG during pregnancy

| Method and dose | Mechanism | Advantages | Disadvantages |
|---|---|---|---|
| Low-fat diet (less than 20% of calories from fat) | Reduction in substrate for exogenous pathway | Efficacious in reduction of plasma TG | Compliance<br>Risk of impaired fetal brain and visual development with <2% if EFA deficiency<br>Isocaloric fat restriction may paradoxically increase fasting TG |
| Admission, NPO, iv therapy (iv D5/0.45 until TG levels fell by half), or TPN (as per dietician) | Carbohydrate ingestion PO leads to greater rise in plasma TG than similar substrate iv | Intravenous calories aid in reversal of maternal weight loss<br>Hospital admission helps with diet compliance | Inconvenience |
| MCT (10–30 g/d) | Transported directly to the liver for oxidation<br>Not incorporated into chylomicrons | Source of calories (8.3 kcal/g compared to 3–4 kcal/g for carbohydrates and protein)<br>May benefit fetal brain myelination | Abdominal discomfort |
| Omega 3 (3–4 g/d) | Suppress lipogenesis<br>Enhances the oxidation of fatty acids<br>Direct activation of LPL | Adverse pregnancy outcome from exposure to these agents appears unlikely | Unpleasant odor |
| Topical sunflower oil (1 tablespoon/d transcutaneous) | Cutaneous administration aids in reversal of biochemical and clinical manifestations of EFA deficiency in infants and adults | May help prevent EFA deficiency in both the mother and fetus | No reports of successful prevention of gestations chylomicronemia |
| Fibrates: gemfibrozil 600 mg twice daily, fenofibrate 145–200 mg once daily) | Activates nuclear transcription factors for up-regulation of LPL transcription and down- regulates the LPL inhibitor apo C-III<br>Limits substrate availability for TG synthesis in the liver<br>Stimulates apo A-I and apo A-II in liver, increasing HDL and thus increasing reverse cholesterol transport | Gemfibrozil: multiple case reports of use during pregnancy with no adverse effects reported<br>Fenofibrate: no teratogenicity has been found in rat model | Variable response partly related to genotype<br>Side effects limited to GI symptoms<br>Safety in pregnancy suggested but not established |
| Niacin (1500–3000 g/d) | Inhibits adipose fatty acid release and induces hepatic $\beta$-oxidation of fatty acids limiting substrate for lipogenesis | Deficiency during human pregnancy was associated with congenital heart disease in the offspring | Recommended upper limits for niacin as supplement in pregnant and lactating women are 30 mg/d for women greater than age 18 yr and 35 mg/d for older women; however, toxicity is unknown<br>Hyperlipidemia starting doses are 1500 mg/d |
| | Human LPL "gain-of-function" variant delivered in vector | Preliminary studies showed reduction of risk of pancreatitis by 70% | Long-term effects unknown<br>Teratogenicity unknown<br>Not approved in any country |

…y mouth; D5/0.45, 5% dextrose in 0.45% sodium chloride; GI, gastrointestinal.


Alys… …demia in Pregnancy, J Clin Endocrinol Metab 97: 2589–2596, 2012

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**Table 1.** Treatment modalities for hypertriglyceridemia.

| Treatment | Dose | Expected response | Reproductive safety | Lactation data |
|---|---|---|---|---|
| Fibric acid derivatives | Micronized fenofibrate 200 mg PO daily<br>Gemfibrozil 600 mg PO twice daily | LDL-C ↓16–27% HDL-C ↑9% TG ↓46–54%[12a] | No teratogenic effects seen in animal reproductive studies.[13] | No published data to date. |
| Omega-3 fatty acids (DHA) | 3–4 g PO daily | HDL-C ↑5–9% TG ↓25–30%[14a,15a] | An RCT did not identify any serious safety concerns related to DHA supplementation for mother or newborn.[16] An observational study did not find any association with PTD, or adverse effect on birthweight.[17] | Compatible. |
| HMG CoA reductase inhibitors | Atorvastatin 5–80 mg PO daily<br>Rosuvastatin 5–20 mg PO daily<br>Pravastatin 10–80 mg PO daily<br>Simvastatin 5–40 mg PO daily | LDL-C ↓20–60% HDL-C ↑5–10% TG ↓10–33%[18a,19a] | Large cohort study did not find a significant teratogenic effect from maternal use of statins in the first trimester.[20] | Transferred into breast milk,[21] limited published data to date. |
| Insulin | Intravenous infusion titrated to serum blood glucose of 5–10 mmol/L[22a] | TG ↓32–48%[22a] | Safe in pregnancy. | Compatible. |
| Heparin | Intravenous infusion (therapeutic anticoagulation)[23] | TG ↓76% after 18 h[23] | No placental transfer due to high molecular weight.[24] | Compatible. |
| Plasmapheresis | Frequency not defined, titrate to desired clinical effect | TG ↓94%, LDL ↓64% and HDL ↑850% after 3 sessions[25a] | Multiple case reports have not demonstrated any safety concerns.[3–7] | No published data to date. |
| Niacin | Extended release: 500 mg qhs, titrated to 1–2 g qhs | LDL-C ↓18% HDL-C ↑29% TG ↓21–24%[26a] | No human studies in pregnancy. | No published data to date. |

LDL-C: low-density lipoprotein cholesterol; HDL: high-density lipoprotein; PTD: preterm delivery; TG: triglycerides; RCT: randomized controlled trial.
[a]Data are from non-pregnancy studies.

Lim R. et Al, Presentation and management of acute hypertriglyceridemic pancreatitis in pregnancy: A case repor. Obstetric Medicine 2015, Vol. 8(4) 200–203