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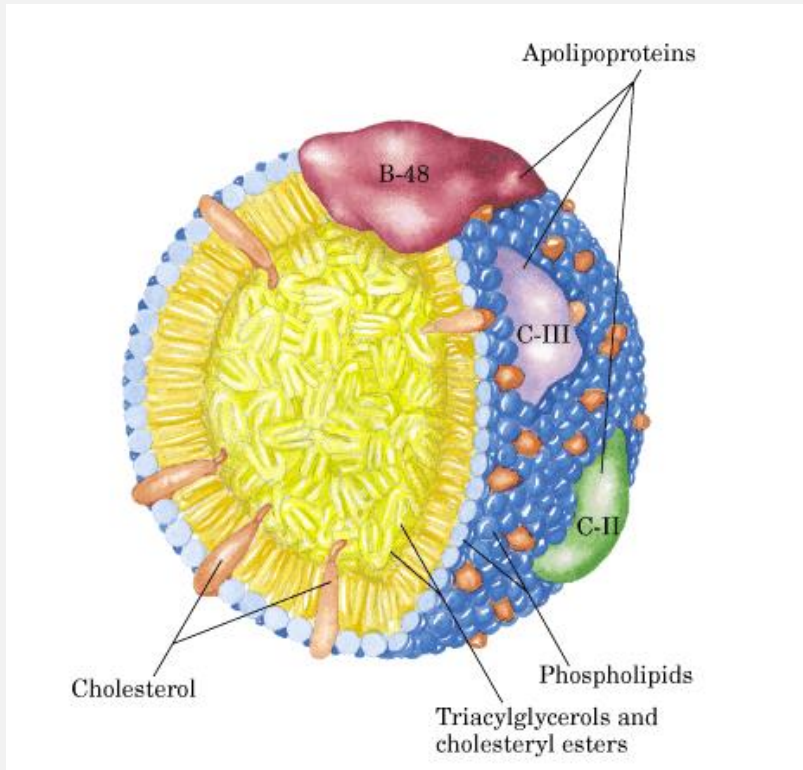
DISLIPIDEMIA Y EMBARAZO

DRA ANA LUISA PEREZ

DR DANIEL MARTIN , DR J.GUILLERMO RODRIGUEZ

BECADA MMF U DE CHILE

METABOLISMO LIPIDICO

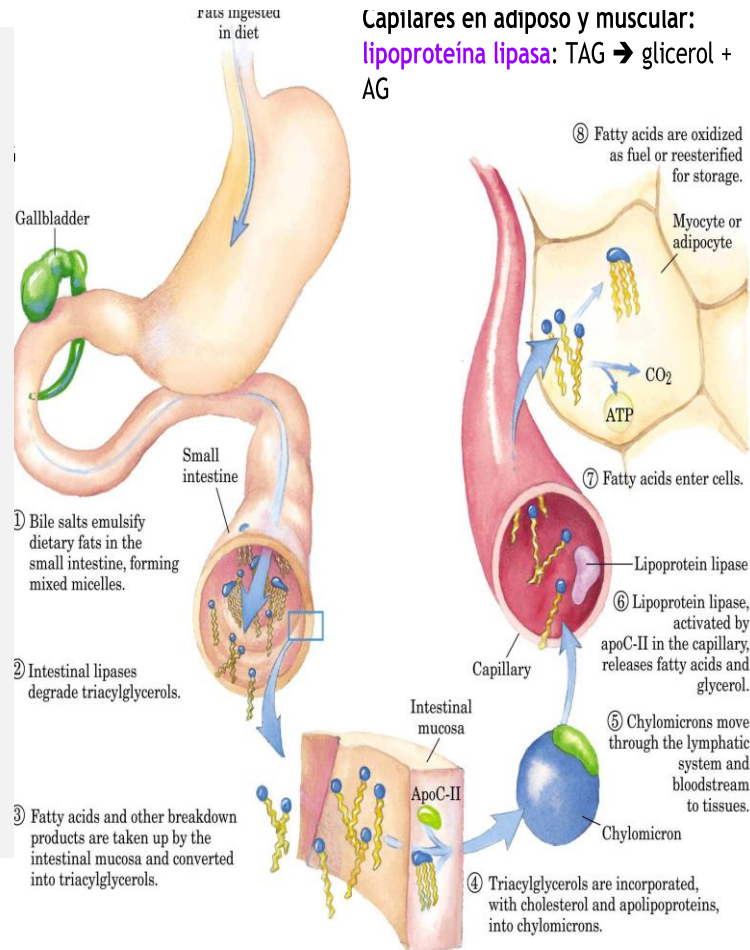


Triglicéridos
Colesterol libre
Colesterol esterificado
Fosfolípidos

Función reserva
energética, estructural
y señalización



METABOLISMO LIPIDICO



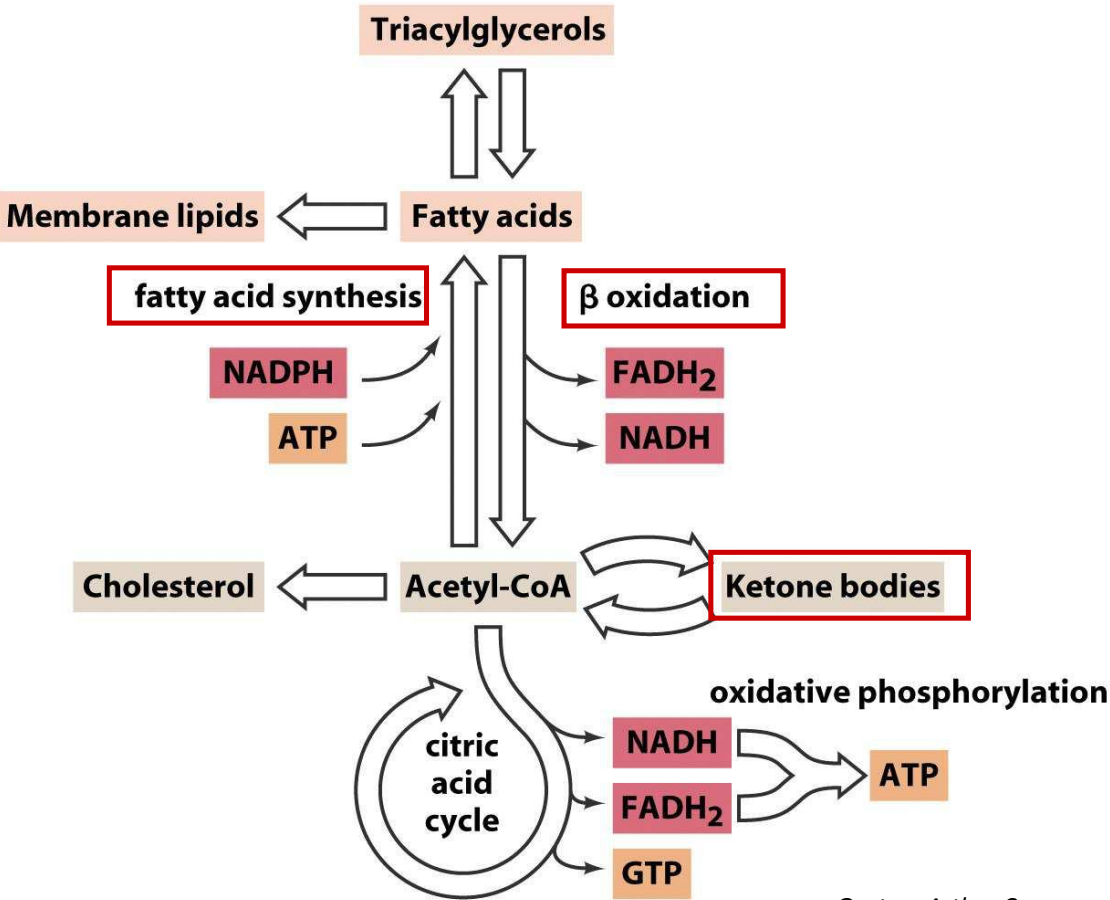
Capilares en adiposo y muscular:
lipoproteína lipasa: TAG → glicerol + AG



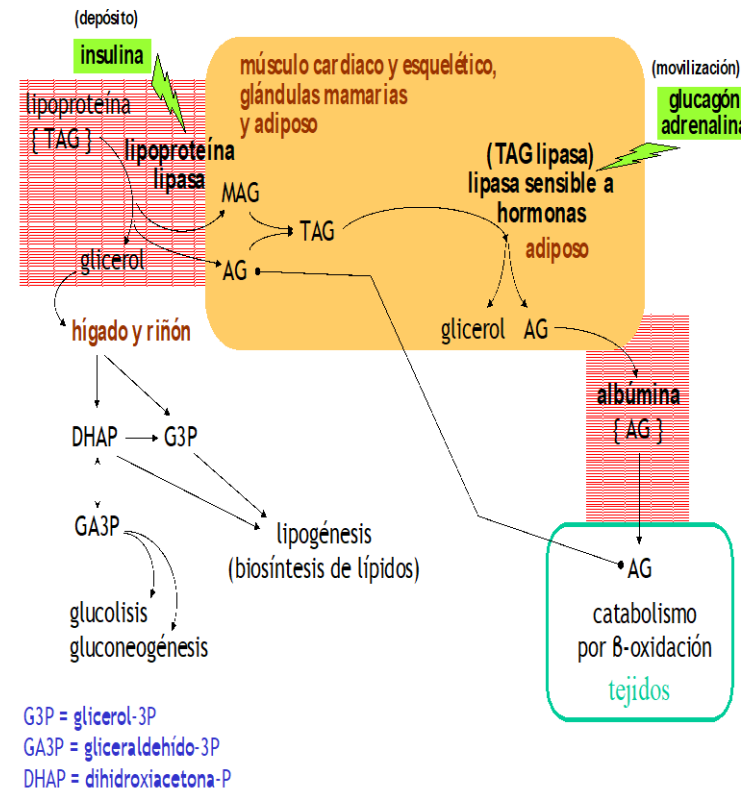
Guyton, Arthur C.

Textbook of medical physiology / Arthur C. Guyton, John E. Hall.—11th ed.

METABOLISMO LIPIDICO



LIPOLISIS: Catabolismo de los triacilgliceroles



Guyton, Arthur C.
 Textbook of medical physiology / Arthur C. Guyton, John E. Hall.—11th ed.

METABOLISMO LIPIDICO



Tabla 1
Composición de los complejos lipoproteicos mayores

Lipoproteína	Origen	Densidad (g/ml)	% proteína	% TG	% PL	% CE	% CL
QM	Intestino	<0,95	1-2	85-88	8	3	1
VLDL	Higado	0,95-1,006	7-10	50-55	18-20	12-15	8-10
IDL	VLDL	1,006-1,019	10-12	25-30	25-27	32-35	8-10
LDL	VLDL	1,019-1,063	20-22	10-15	20-28	37-48	8-10
HDL2	Intestino Higado QM, VLDL	1,063-1,125	33-35	5-15	32-43	20-30	5-10
HDL3	Intestino Higado QM, VLDL	1,125-1,21	55-57	3-13	26-46	15-30	2-6

QM = quilomicrón; VLDL = very low density lipoprotein; IDL = intermediate density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein.



Guyton, Arthur C.

Textbook of medical physiology / Arthur C. Guyton, John E. Hall.—11th ed.

PERFIL LIPIDICO EN EMBARAZO



La primera mitad del embarazo , prevalece el metabolismo anabólico con hiperfagia y aumento de los depósitos grasos

El tercer trimestre aumenta la lipólisis y disminuye la acumulación de grasa

PERFIL LIPIDICO EN EMBARAZO



Aumenta la producción de glucosa por el hígado, pero al mismo tiempo la glicemia tiende a disminuir por hemodilución y paso transplacentario

IR: Lactógeno placentario , progesterona , prolactina , cortisol y TNF alfa

La gestante normalmente sensible a la insulina aumenta su insuliniresistencia e un 10% en el embarazo , la insulino resistente hasta un 40%

PERFIL LIPIDICO EN EMBARAZO



El colesterol es imprescindible para
La formación de membranas, síntesis de esteroides
y diferenciación celular y es necesario para el
desarrollo embrionario y fetal

Aunque el feto es capaz de sintetizar su propio
colesterol, existe también un aporte exógeno de
colesterol de la circulación materna a través de la
placenta.

PERFIL LIPIDICO EN EMBARAZO



Hasta hace poco se pensaba que el saco vitelino y el feto sintetizaban todo el colesterol de novo

Actualmente se han identificado receptores en trofoblasto : (LDL) (LDLRs), LDLR, scavenger A, and high-density lipoprotein (HDL)–binding scavenger receptors B1 (SR-B1s) y ligandos Apo B y Apo E

PERFIL LIPIDICO EN EMBARAZO



Historicamente la dislipidemia se ha considerado fisiológica en el embarazo

Evidencia actual sugiere que alteraciones en el perfil lipídico materno se relaciona con presencia de placas de ateroma a los 6 meses en aorta de los hijos de madres dislipidemicas

Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest

1997;100(11):2680-90.

PERFIL LIPIDICO EN EMBARAZO



Los embarazos han aumentado en el grupo de mujeres entre 30 y 40 años

Aproximadamente el 50% son no planificados

45% de las mujeres se embaraza con sobrepeso u obesa , y el 43% gana mas peso del recomendado

Rol del ginecoobstetra en prevención y planificación

PERFIL LIPIDICO EN EMBARAZO



Los niveles de lípidos han sido ampliamente estudiados durante el embarazo , aún así no existen curvas estandarizadas para embarazadas

El embarazo es un estado de insulinoresistencia que se refleja en el perfil lipídico materno

Los niveles de TG , CT y LDL aumentan progresivamente durante el embarazo y de mayor manera el tercer trimestre

Habitualmente en promedio los niveles de TG y CT no excede los 250 mg / dl , en embarazos con factores de riesgo pueden llegar a niveles mayores a 300 mg /dl

PERFIL LIPIDICO EN EMBARAZO



Las variaciones en el perfil lipídico son independientes de edad , raza e IMC

Recupera con postparto y se acelera con la lactancia materna

PERFIL LIPIDICO EN EMBARAZO



Estrogenos : aumentan los niveles de triglicéridos estimulando la producción de VLDL e inhibiendo LPL hepática y periférica
Progesterona , se opone a esta acción , aumentando la insulinoresistencia

PERFIL LIPIDICO EN EMBARAZO

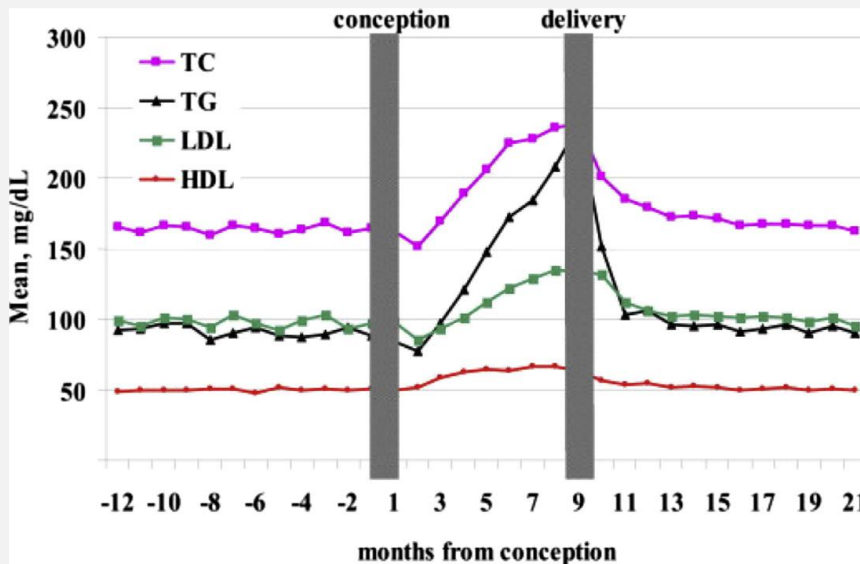


Fig. 1. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) 1 year before, during, and after pregnancy. (From Wiznitzer A, Mayer A, Novack V, et al. Association of lipid levels during gestation with preeclampsia and gestational diabetes mellitus: a population-based study. *Am J Obstet Gynecol* 2009;201(5):482.e1–8; with permission.)

Wild et al., *womans health considerations for lipids management. Endocrinol Metab Clin N Am* 45 (2016) 65–85
<http://dx.doi.org/10.1016/j.ecl.2015.09.005>

EVALUACION DISLIPIDEMIA EN EMBARAZO



Dislipidemia familiar :

Con historia clínica y hallazgos al examen físico ,
habitualmente niveles mayor a 500 mg /dl de TG

Disminución ingesta calórica , disminución porcentaje grasas ,
uso de fibratos , insulina

Causas medicas:

Hipotiroidismo, consumo de OH, HBPM, glucocorticoides ,
medicamentos psicotropicos, enfermedad renal, diabetes

ROL DE LA DISLIPIDEMIA EN EL EMBARAZO



Comportamiento de los lípidos durante la gestación y su relación con acontecimientos obstétricos desfavorables

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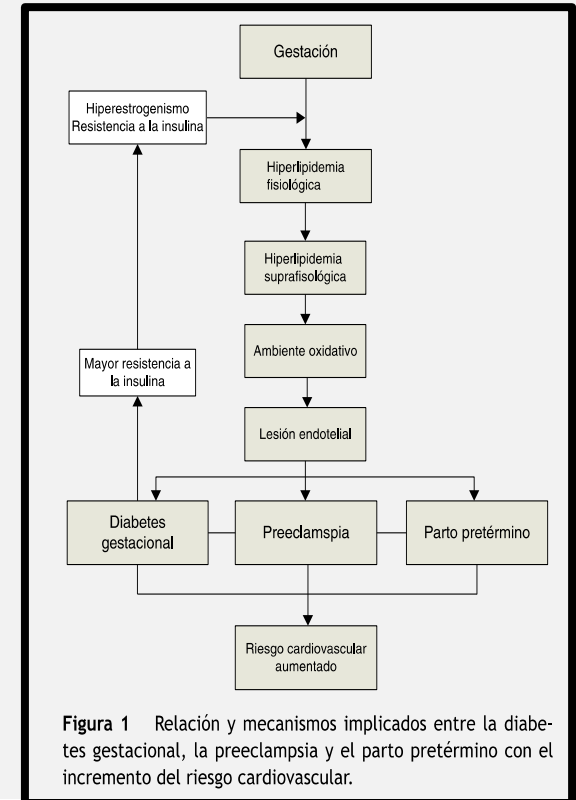
^a Servicio de Ginecología y Obstetricia, Hospital del Mar, Barcelona, España

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ROL DE LA DISLIPIDEMIA EN EL EMBARAZO



- **LIPIDOS Y PREECLAMPSIA:**
 - ASOCIACIÓN ENTRE PE Y RIESGO CV
 - ASOCIACIÓN ESPECÍFICA CON HIPERTRIGICERIDEMIA POR STRESS OXIDATIVO
 - ESTUDIOS CASO CONTROL Y COHORTE HAN MOSTRADO AUMENTO DE CONCENTRACIONES DE TG EN MUJERES PE VS SANAS , MAS AUN CON NIVELES DE LDL ELEVADOS

PERFIL LIPIDICO EN EMBARAZO



Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study

Tanja G. M. Vrijkotte, Náthalie Krukziener, Barbara A. Hutten, Karlijn C. Vollebregt, Manon van Eijsden, and Marcel B. Twickler

Context: Elevated lipid levels during late pregnancy are associated with complications and adverse outcome for both mother and newborn. However, it is inconclusive whether a disturbed lipid profile during early pregnancy has similar negative associations.

Objective: Our objective was to investigate whether nonfasting maternal total cholesterol and triglyceride levels during early pregnancy are associated with six major adverse pregnancy outcomes.

Methods: Data were derived from the Amsterdam Born Children and Their Development (ABCD) cohort study. Random blood samples of nonfasting total cholesterol and triglyceride levels were determined during early gestation (median = 13, interquartile range = 12–14 wk). Outcome measures were pregnancy-induced hypertension (PIH), preeclampsia, preterm birth, small/large for gestational age (SGA/LGA), and child loss. Only nondiabetic women with singleton deliveries were included; the baseline sample consisted of 4008 women. Analysis for PIH and preeclampsia were performed in nulliparous women only (n = 2037).

Results: Mean (SD) triglyceride and total cholesterol levels were 1.33 (0.55) and 4.98 (0.87) mmol/liter, respectively. The incidence of pregnancy complications and perinatal outcomes were as follows: PIH, 4.9%; preeclampsia, 3.7%; preterm birth, 5.3%; SGA, 9.3%; LGA, 9.3%; and child loss, 1.4%. After adjustments, every unit increase in triglycerides was linearly associated with an increased risk of PIH [odds ratio (OR) = 1.60, $P = 0.021$], preeclampsia (OR = 1.69, $P = 0.018$), LGA (OR = 1.48, $P < 0.001$), and induced preterm delivery (OR = 1.69, $P = 0.006$). No associations were found for SGA or child loss. Total cholesterol was not associated with any of the outcome measures.

Conclusions: Elevated maternal triglyceride levels measured during early pregnancy are associated with pregnancy complications and adverse pregnancy outcomes. These results suggest that future lifestyle programs in women of reproductive age with a focus on lowering triglyceride levels (*i.e.* diet, weight reduction, and physical activity) may help to prevent hypertensive complications during pregnancy and adverse birth outcomes. (*J Clin Endocrinol Metab* 97: 3917–3925, 2012)

Se excluyeron diabeticas ,
multiples y EG no segura
4000 mujeres

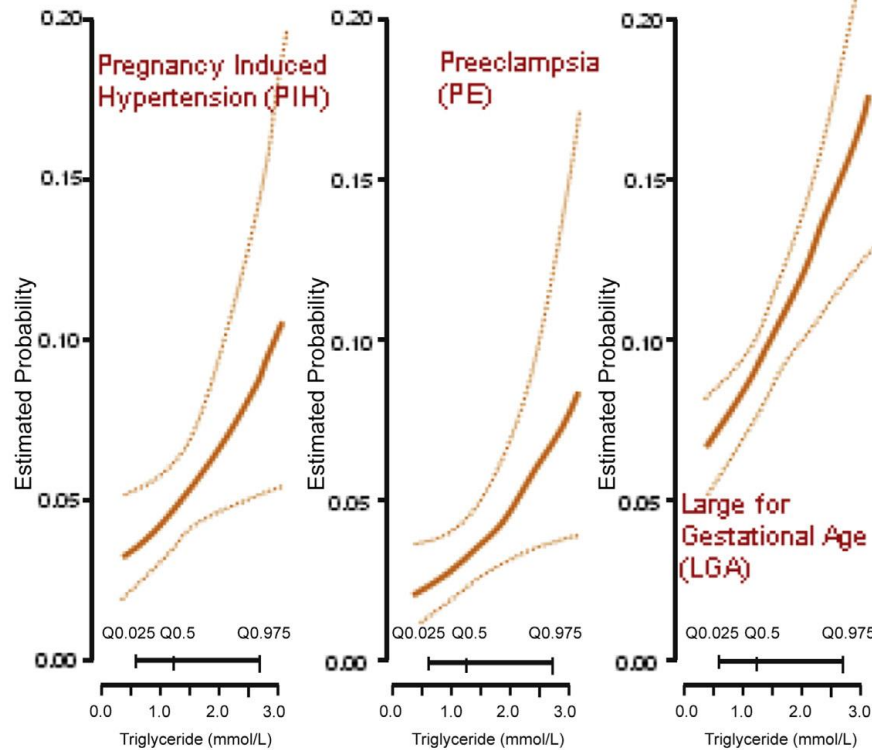
Se correlaciono TG con
HIE; PE ; PP NO
ESPONTANEO Y GEG
No hubo diferencias con
PEG y pérdida del
embarazo
CT no se relacionó

Tanja g m. maternal lipid profile during early pregnancy and pregnancy complications and outcomes: The ABC study J Clin Endocrinol Metab 97: 3917–3925, 2012)

PERFIL LIPIDICO EN EMBARAZO



The estimated probability for PIH, preeclampsia (PE), and LGA



TG levels in the first trimester of pregnancy are a significant, but modest, contributor in the expression of PIH, PE, induced preterm birth, and children to be born Large for Gestational Age. With this observation, inclusion of a lipid profile may be considered early in pregnancy & in the preconception screening.

1 mmol/L of TG = 135 mg/dL
2 mmol/L = 176 mg/dL

Q0.025, Q0.5, and Q0.975 represent the 2.5th, 50.0th, 97.5th percentiles of the studied population.

Fig. 3. First trimester maternal triglyceride relationships. (Adapted from Vrijkotte TG, Krukziener N, Hutten BA, et al. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. J Clin Endocrinol Metab 2012;97(11):3917–25.)

Tanja g m. maternal lipid profile during early pregnancy and pregnancy complications and outcomes: The ABC study J Clin Endocrinol Metab 97: 3917–3925, 2012)

ROL DE LA DISLIPIDEMIA EN EL EMBARAZO



- **LIPIDOS Y PREECLAMPSIA:**
 - ESTUDIO PROSPECTIVO CASO CONTROL NO LOGRÓ DEMOSTRAR TAL ASOCIACIÓN

Arch Gynecol Obstet (2013) 288:49–55
DOI 10.1007/s00404-013-2750-y

MATERNAL-FETAL MEDICINE

Plasma lipids and lipoproteins during pregnancy and related pregnancy outcomes

Turgay Emet · Işık Üstüner · Seda Güvendağ Güven · Gülşah Balık ·
Ülkü Mete Ural · Yeşim Bayoğlu Tekin · Şenol Şentürk · Figen Kır Şahin ·
Ayşe Filiz Avcı

*Ferriols E, et al. Comportamiento de los lípidos durante la gestación y su relación con acontecimientos obstétricos desfavorables. Clin Invest Arterioscl. 2015.
<http://dx.doi.org/10.1016/j.arteri.2015.04.003>*

PERFIL LIPIDICO EN EMBARAZO



Arch Gynecol Obstet (2013) 288:49–55
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MATERNAL-FETAL MEDICINE

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Ayşe Filiz Avşar

- Objetivo : Estudiar el efecto de los cambios del perfil lipídico materno en relación a crecimiento y desarrollo fetal pronóstico y resultados en el embarazo
- Metodo : Prospectivo , longitudinal , un centro se midió concentración de TG , CT, HDL y LDL antes de las 14 y después de las 28 semanas, el análisis incluyó el status medico social y demográfico de las pacientes
- Outcome primario: relación del perfil lipídico con peso fetal al nacer, peso al tercer mes de vida y complicaciones del embarazo como PE, DG, RCIU y PP

PERFIL LIPIDICO EN EMBARAZO



Los niveles de TG , CT y LDL aumentaron durante el embarazo

Los niveles de TG se correlacionaron directamente con el peso al nacer , no así al tercer mes

No hubo asociación con PE ni con DG , si inversamente de niveles de TG con PP

PERFIL LIPIDICO EN EMBARAZO



DIABETES Y PERFIL LIPÍDICO

DOI: 10.1111/1471-0528.13261
www.bjog.org

Systematic review

Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis

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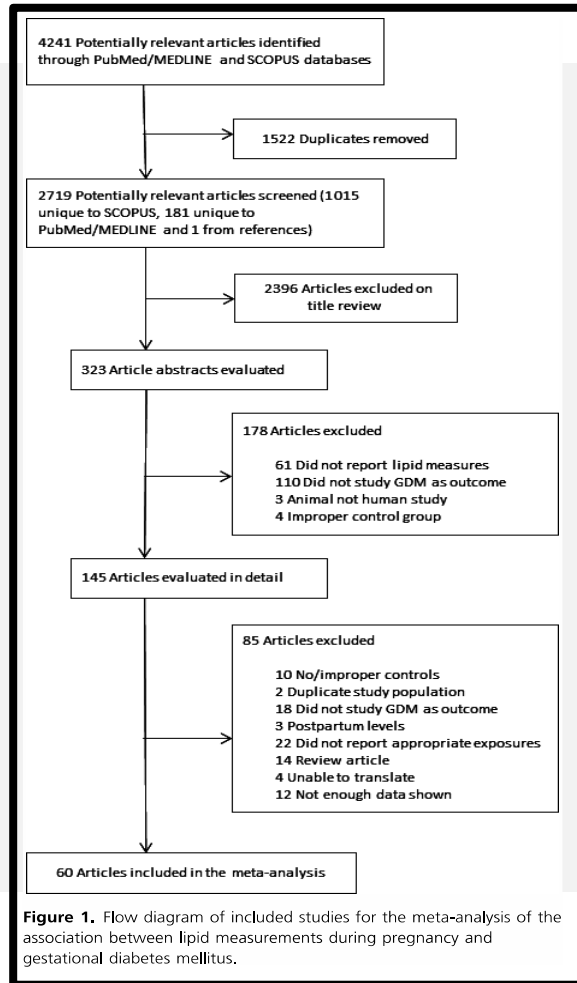
Accepted 4 November 2014. Published Online 22 January 2015.

PERFIL LIPIDICO EN EMBARAZO



- Objetivos : evaluar la variación de lípidos en embarazo y DG
- Criterios de selección: Con grupo control y al menos una medición de CT, LDL, HDL y TG
- Los niveles de triglicéridos fueron significativamente más altos en todas las etapas del embarazo en mujeres que desarrollaron diabetes
- Los niveles de HDL fueron menores significativamente solo en segundo y tercer trimestre
- No hubo diferencias al agregar mediciones de colesterol total y LDL

PERFIL LIPIDICO EN EMBARAZO



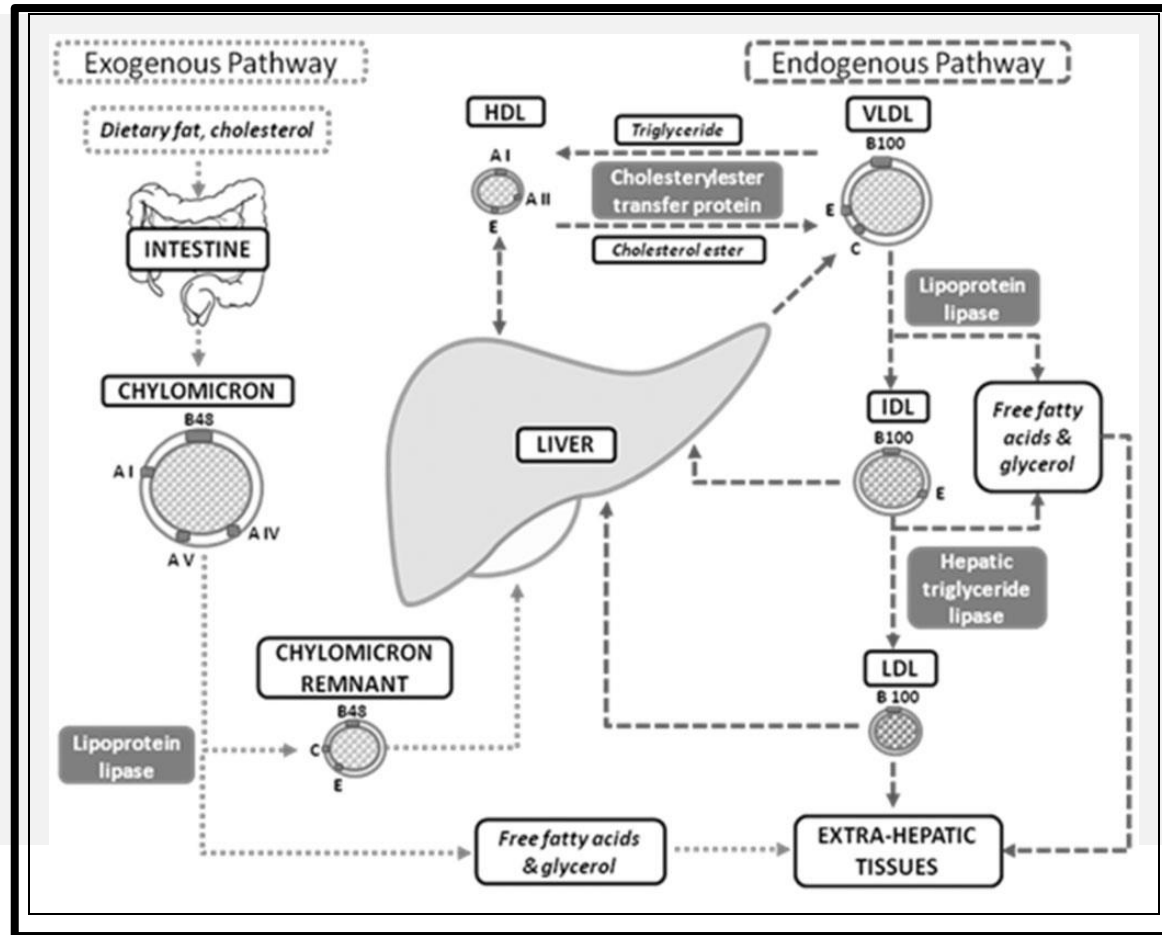
Se analizaron un total de 13886 mujeres, 4186 con DG y 9718 sin .

Los niveles de triglicéridos fueron significativamente más altos en todas las etapas del embarazo en mujeres que desarrollaron diabetes

TRANSPORTE PLACENTARIO



HIPERTRIGLICERIDEMIA Y EMBARAZO



HIPERTRIGLICERIDEMIA Y EMBARAZO, PANCREATITIS AGUDA



Mecanismo no bien dilucidado eventual activación de lipasas pancreaticas promovido por el ambiente rico en triglicéridos, lo que liberaría ácidos grasos que dañan el endotelio y células acinares pancreaticas

HIPERTRIGLICERIDEMIA Y EMBARAZO PANCREATITIS AGUDA



Incidencia 3-7/10.000

Clasicamente se describía una mortalidad materna y fetal alta que ha disminuido por los cuidados actuales

HIPERTRIGLICERIDEMIA Y EMBARAZO

PANCREATITIS AGUDA



Mujeres con factores de riesgo de hipertrigliceridemia deben recibir consejería preconcepcional .

Debe buscarse didrigidamente hipertrigliceridemia en aquellas con factores de riesgo

HIPERTRIGLICERIDEMIA Y EMBARAZO, PANCREATITIS AGUDA

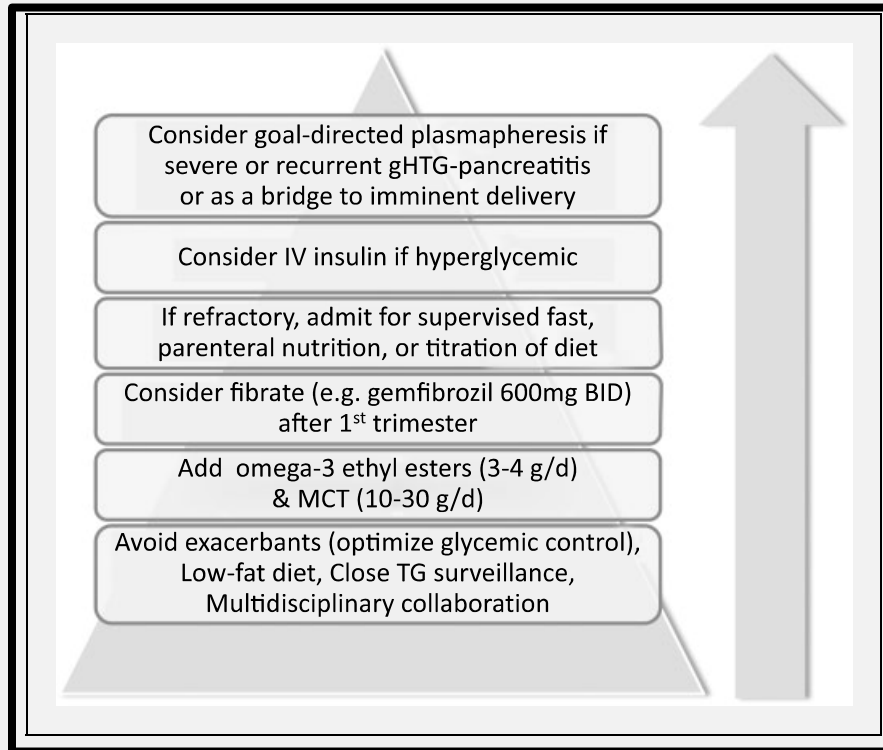


Table 1. Primary and secondary factors contributing to severe gestational hypertriglyceridemia.

Predisposing factors	Examples
Primary (genetic) factors	
• Increased production	■ Familial combined hyperlipidemia (FCH) ■ Familial hypertriglyceridemia (FHTG)
• Ineffective lipolysis	■ Familial chylomicronemia disorders
• Decreased remnant clearance	■ Familial dysbetalipoproteinemia
Secondary (non-genetic) factors	
• States of altered physiology	■ Insulin-resistant states (e.g. untreated/poorly-controlled diabetes mellitus) ■ Hypothyroidism ■ Nephrotic syndrome
• Medications/toxins	■ Glucocorticoids ■ Beta-blockers ■ Protease inhibitors ■ Alcohol



HIPERTRIGLICERIDEMIA Y EMBARAZO, PANCREATITIS AGUDA



NIVELES 11,4 MMOL/LT SE ASOCIAN CON MAYOR RIESGO DE PANCREATITIS

TERAPIA ESCALONADA :
DIETA Y EJERCICIO
SI CON MEDIDAS HABITUALES CONTINÚA EN ALZA CONSIDERAR HOSPITALIZACION

HIPERTRIGLICERIDEMIA Y EMBARAZO, PANCREATITIS AGUDA



Table 2. Management of gestational hypertriglyceridemia.

	Mechanism	Benefit	Risk	Key references
Low fat diet < 20% of calories from fat/day	<ul style="list-style-type: none"> Reduce substrates for exogenous TG synthesis pathway 	<ul style="list-style-type: none"> Effective in plasma TG lowering 	<ul style="list-style-type: none"> Difficult patient adherence Risk of maternal weight loss and fetal essential fatty acid (EFA) deficiency 	Sanderson ⁵⁸ Ma ¹⁰ Mizushima ²¹ Shenhav (2002) ¹³ Al-Shali ⁵¹ Tsai ²⁸ Abu Musa ³⁰ Basaran ² Sivakumaran ⁵³ Goldberg ²⁵ Basar ⁵⁴ Han ¹¹ Gupta ⁵⁶
Omega-3-acid ethyl esters 3 to 4g/d orally	<ul style="list-style-type: none"> Reduce hepatic TG synthesis Increase fatty acid oxidation in the liver and skeletal muscle Enhance LPL activity 	<ul style="list-style-type: none"> Reduce TG by 25–50% via several mechanisms Helps avoid deficiency of key omega-3 fatty acids including DHA and EPA 	<ul style="list-style-type: none"> Fishy taste, mild gastrointestinal side effects (e.g. burping) May not lower TG quickly enough in acute setting 	Goldberg ²⁵ Basar ⁵⁴ Han ¹¹
Medium-chain triglycerides (MCT) 10 to 30g/d orally Available as supplement but also in coconut oil, palm kernel oil, butter	<ul style="list-style-type: none"> Provide nutritional support with rapid small intestine absorption and direct transport of TG via portal vein to liver for oxidation without CM formation Mitigates the increase in dietary CHO in an isocaloric diet 	<ul style="list-style-type: none"> Densely caloric (8.3 kcal/g for MCT vs. 3–4 kcal/g for carbohydrate and protein) Potential positive impact on fetal brain development 	<ul style="list-style-type: none"> Gastrointestinal side effects (e.g. abdominal discomfort, diarrhea, nausea, intestinal gas) 	Mizushima ²¹ Shenhav ¹³
Fibrates e.g. Gemfibrozil 600mg twice-daily	<ul style="list-style-type: none"> Transcription regulation via (+)PPARα Increase LPL-mediated catabolism of VLDL particles by up-regulation of LPL, apoA-I, and apoA-II Decrease apoB and VLDL production by down-regulation of apoCIII expression 	<ul style="list-style-type: none"> Effective gradual reduction in TG in many genetic forms of HTG, although response genotype dependent 	<ul style="list-style-type: none"> Safety in pregnancy controversial May not lower TG quickly enough in acute setting 	Gemfibrozil: Al-Shali ⁵¹ Tsai ²⁸ Goldberg ²⁵ Fenofibrate (with niacin): Abu Musa ³⁰
Parenteral nutrition	<ul style="list-style-type: none"> Less increase in TG from iv carbohydrate ingestion compared to enteral carbohydrate nutrition 	<ul style="list-style-type: none"> Provides source of calories Helps prevent/reverse maternal weight loss 	<ul style="list-style-type: none"> Typically requires hospitalization 	Sanderson ⁵⁸ Shenhav ¹³ Al-Shali ⁵¹ Goldberg ²⁵
Insulin Intravenous most often	<ul style="list-style-type: none"> Rapid and potent LPL activator 	<ul style="list-style-type: none"> Immediate dramatic TG-lowering effect 	<ul style="list-style-type: none"> No clear role for euglycemic patients (risk of hypoglycemia) 	Al-Shali ⁵¹ Basaran ² Basar ⁵⁴
Plasmapheresis	<ul style="list-style-type: none"> Rapid removal of TG-rich lipoproteins Removal of inflammatory mediators/cytokine levels in acute pancreatitis 	<ul style="list-style-type: none"> Immediate dramatic TG-lowering effect 	<ul style="list-style-type: none"> Limited availability High cost Risk of infection/thrombosis of plasmapheresis catheter line Transient effect 	Ma ¹⁰ Sivakumaran ⁵³ Basar ⁵⁴ Gupta ⁵⁶ Safi ⁵⁵

CHO: carbohydrate; CM: chylomicron; DHA: docosahexaenoic acid; EFA: essential fatty acid; EPA: eicosapentaenoic acid; MCT: medium-chain triglycerides; TG: triglyceride; LPL: lipoprotein lipase; VLDL: very low density lipoprotein.

HIPOLIPEMIANTE



Accepted Manuscript

The Risks of Statin Use in Pregnancy: A Systematic Review

Dean G. Karalis, MD, FACC, FAHA, FNLA, Alethea N. Hill, PhD, ACNP-BC, RN, ANP-BC, Shari Clifton, MLIS, AHIP, Robert A. Wild, MD, MPH, PhD, FNLA



PII: S1933-2874(16)30234-3

DOI: [10.1016/j.jacl.2016.07.002](https://doi.org/10.1016/j.jacl.2016.07.002)

16 estudios incluidos , 5 series de casos , 3 cohortes , 1 RC y 4 RS

134 casos , 85% de fetos normales , 4% anomalías congénitas , 8% aborto espontáneo , 89% expuestos en primer trimestre

RC: pravastatina sin efectos deletéreos .

HIPOLIPEMIANTE



Table 1
Lipid level-lowering agents and pregnancy classification

Lipid Level-lowering Agent	Pregnancy Class
Statins	X
Fibrates	C
Ezetimibe	C
Niacin	C
Cholestyramine	C
Colesevelam	B
Mipomersen	B

- Wild et al., womans health considerations for lipids management. *Endocrinol Metab Clin N Am* 45 (2016) 65–85
- <http://dx.doi.org/10.1016/j.ecl.2015.09.005>