UMBERTO I POLICLINICO DI ROMA

Università degli studi di Roma "Sapienza"
Dipartimento di Medicina Materno-Infantile e di Scienze Urologiche

PREGNANT FH WOMEN: STATE OF THE ART AND PERSPECTIVES

G. Perrone
E. Marcoccia
M. Candelieri

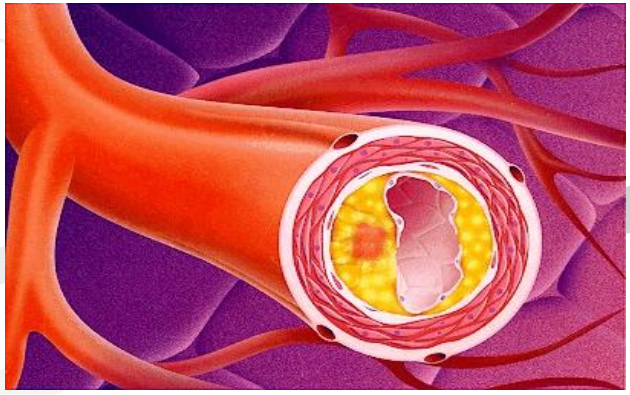
Roma, 3-4 Maggio 2017

FH and Pregnancy

❖THE OVERALL INCIDENCE OF FAMILIAR HYPERCHOLESTEROLEMIA : 2,1/1000

HeFH: 1/500
HoFH: 1/1.000.000

HoFH PATIENTS HAVE AN INCREASED RISK (20-FOLD) TO DEVELOPING PREMATURE ATHEROSCLEROSIS AND CHD



HoFH and Pregnancy

Serum cholesterol may increase by as much as 25–50% and triglycerides (TG) may more than double in the third trimester of pregnancy.
These lipid changes are at least partly explained by hormonal changes.
Subjects with familial hypercholesterolemia (FH) have only 50% of the LDL receptors compared to healthy subjects and thus much higher total- and LDL serum cholesterol concentrations.

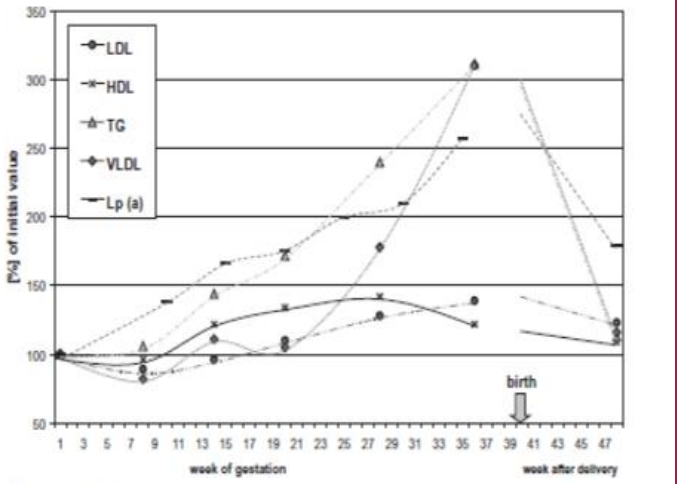
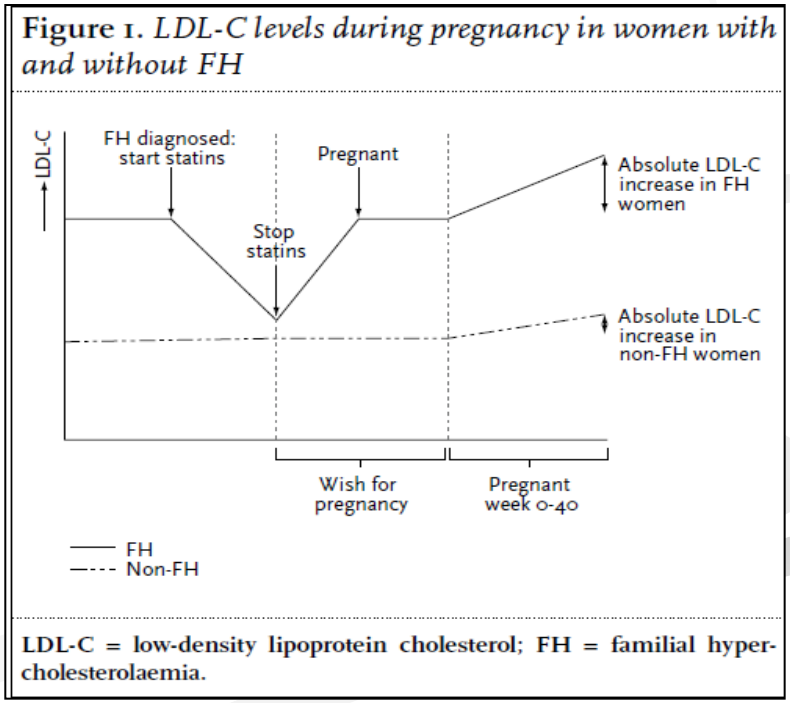


FIG. 2. Potential changes of the blood concentrations of low-density lipoprotein (LDL), high density lipoprotein (HDL), very low-density lipoprotein (VLDL) cholesterol, triglycerides (TG), and lipoprotein (a) (Lp(a)) during normal pregnancy [% of initial value] (modified from 18,19,21,22).

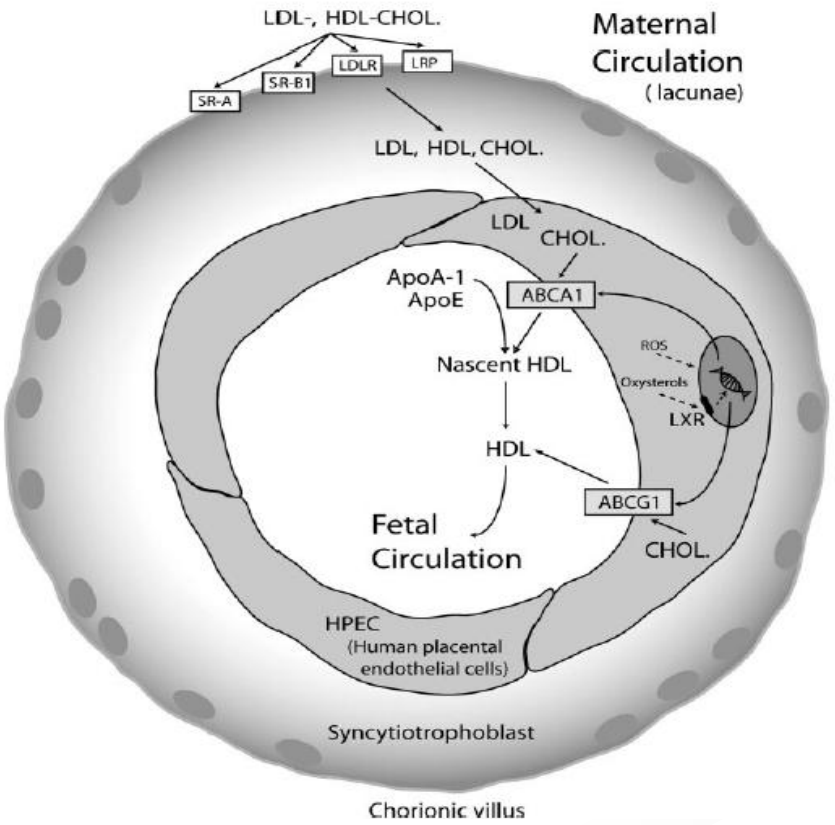
Klingel R. et al.2003



Amundsen A.L. et al. 2006

Maternal-Fetal Cholesterol Transport

Cholesterol is of vital importance for fetal development as a key constituent of cell membranes, a precursor of steroid hormones and metabolic regulators, and a modulator of hedgehog signaling



REGULATION/EFFECT:

Beneficial:

Driven by fetal needs (fetal genetic defects: insufficient chol in Smith-Lemli Opitz S.)

Physiologic changes during pregnancy:

- Decreasing fetal cholesterol levels
- Increasing independence from maternal regulation
- Effect of gestational age on placental cell function (?)

Pathogenic:

Developmental programming of cardiovascular disease by maternal hypercholesterolemia, obesity, gestational metabolic syndrome, diabetes or other factors

Palinski W. Maternal-Fetal Cholesterol Transport in the Placenta. Good, Bad and Target for Modulation. Circulation Reasearch 2009

HeFH and Pregnancy

❖WOMEN WITH HeFH WHO ARE PLANNING A PREGNANCY MUST REMAIN WITHOUT THERAPY (STATIN) FROM ONE MONTH BEFORE STOPPING CONTRECEPTION UNTIL BREASTFEEDING IS COMPLETED

❖DURING PREGNANCY ONLY MONITORING OF CHOLESTEROL VALUES IS REQUIRED

❖IF BOTH PARTNERS HAVE HeFH A GENETIC CONSULTATION IS NECESSARY AND IF REQUIRED INVASIVE GENETIC DIAGNOSIS OF THE FETUS

PREGNANCY IS CONTROINDICATED IN HeFH PATIENTS WITH ISCHEMIC CARDIAC DISAESE

TOLEKEYTE 2011, RUSSI 2015

HeFH and pregnancy: outcomes

Pregnancy Outcomes in Familial Hypercholesterolemia
A Registry-Based Study

Ieva Toleikyte, MSc; Kjetil Retterstøl, MD; Trond Paul Leren, MD; Per Ole Iversen, MD

- RETROSPECTIVE STUDY
- PERIOD OF STUDY: 1967-2006
- 1093 PATIENT WITH GENETIC DIAGNOSIS OF HeFH
- 2314 NEWBORNS

- EVALUATION OF OBSTETRIC MATERNAL AND NEONATAL OUTCOME

	FH Population		General Population			
	%	N	%	N	OR (95% CI)	*P*
Prematurity						
All births	6.8	2184	6.2	2 304 067	1.11 (0.94–1.31)	0.23
Singletons	5.8	2142	5.7	2 152 740	1.02 (0.85–1.22)	0.85
First singletons	6.4	904	6.5	890 790	1.04 (0.81–1.33)	0.78
Multipara singletons	5.4	1238	5.2	1 261 950	0.99 (0.76–1.30)	0.96
Low birth weight						
All births	5.0	2316	5.2	2 330 590	0.96 (0.79–1.15)	0.64
Singletons	4.2	2274	4.2	2 270 281	0.99 (0.81–1.22)	0.95
First singletons	5.4	961	5.1	937 572	1.06 (0.80–1.41)	0.67
Multipara singletons	3.3	1313	3.6	1 332 709	0.92 (0.68–1.24)	0.57
Congenital malformations						
All births	3.3	2319	3.2	2 337 646	1.09 (0.87–1.37)	0.45
Singletons	3.4	2277	3.2	2 274 139	1.09 (0.87–1.36)	0.46
First singletons	4.1	962	3.6	939 109	1.15 (0.83–1.58)	0.40
Multipara singletons	3.0	1315	2.9	1 335 030	1.03 (0.75–1.42)	0.85

FH indicates familial hypercholesterolemia; OR, odds ratio; and CI, confidence interval.

WOMEN WITH HeFH DO NOT APPEAR TO HAVE A HIGHER RISK OF PRETERM DELIVERY OR OF HAVING INFANTS WITH LOW BIRTH WEIGHT OR CONGENITAL MALFORMATIONS THAN WOMEN IN GENERAL, BUT, ALTHOUGH THIS IS UNLIKELY, SOME UNDETECTED BIAS MAY OBSCURE THE REAL DIFFERENCES.

Toleikyte I. 2011

HoFH and Pregnancy

- The combination of PREGNANCY with HoFH can be fatal with an estimated *30%* possibility of acute coronary morbidity in ***mother*** *or* ***child***
- Hemodynamic stress during pregnancy may exacerbate **pre-existing cardiovascular lesions** and precipitate acute events, to the extent that some report HoFH as a ***possible contraindication for pregnancy.***

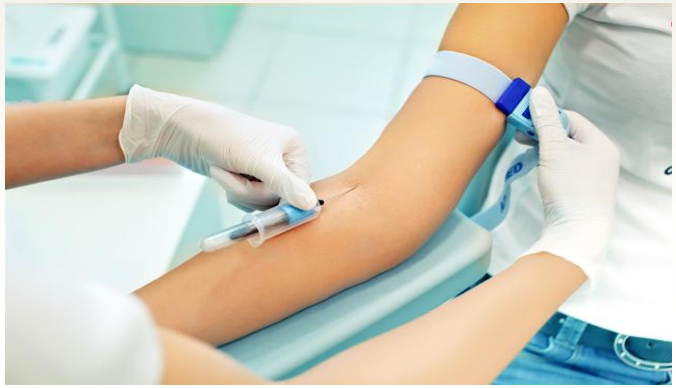
Acute atherosclerosis might affect uteroplacental circulation leading to insufficiency, which could contribute to associated ***pregnancy complications (IUGR, PE).***

DETAILED PRECONCEPTIONAL CV ASSESSMENT SHOULD BE PERFORMED IN HoFH PATIENTS WHO DESIRE TO BECOME PREGNANT AND THIS SHOULD GUIDE THEIR MANAGEMENT.

Blaha M. et al 2015, Russi 2015

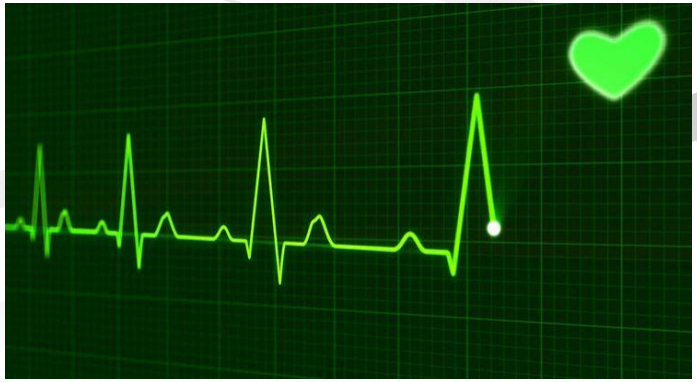
HoFH and Pregnancy

It's still true?



NOWADAYS HoFH PATIENT PROGNOSIS IS IMPROVED:

- EARLY DIAGNOSIS
- INCREASED THERAPEUTIC CHOICES AND EFFICACY OF THESE TREATMENTS
- BETTER VASCULAR CONDITIONS OF HoFH PATIENTS UNDER CONTINUOUS TREATMENT AND SURVEILLANCE

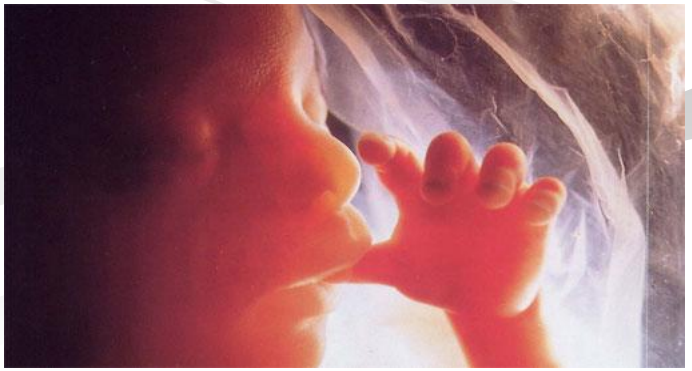


THE PRE-PREGNANCY CARDIOVASCULAR CONDITIONS ARE IMPORTANT

HoFH and Pregnancy

HoFH IS COULD LEAD TO SEVERE COMPLICATIONS DURING PREGNANCY

- **PREGNANCY OUTCOME**
- **MATERNAL OUTCOME**
- **FETAL/NEONATAL OUTCOME**



HoFH and pregnancy: outcomes

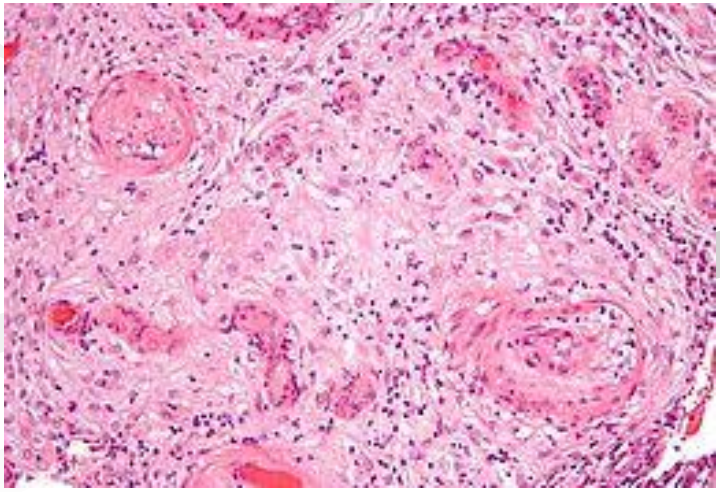
PREGNANCY

- VERY ELEVATED CHOLESTEROL LEVELS CAN BE ASSOCIATED WITH ABNORMAL **UTERO-PLACENTAL VASCULAR RESISTANCE AND INTRA UTERINE GROWTH RESTRICTION**

- IMPAIRMENTS OF LIPOPROTEIN METABOLISM, OXIDATIVE STRESS AND REDUCED ANTIOXIDANT DEFENCE ENHANCE FREE RADICAL MEDIATED MEMBRANE LIPID PEROXIDATION, POSSIBLY CAUSING **VASCULAR ENDOTHELIAL DAMAGE AND LEADING TO A PREECLAMPTIC STATE**

- INCRESED BLOOD VISCOSITY AND MICROCIRCULATION ALTERATIONS CONTRIBUTE TO BOTH **FETAL GROWTH RESTRICTION AND PREECLAMPTIC STATE**

G. Russi 2015



HoFH and pregnancy: outcomes

Placenta 36 (2015) 895–902

Cross-sectional and longitudinal lipid determination studies in pregnant women reveal an association between increased maternal LDL cholesterol concentrations and reduced human umbilical vein relaxation

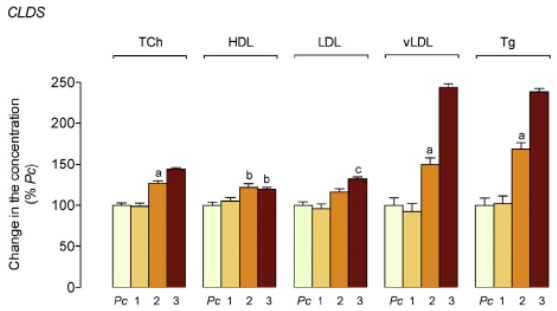
A. Leiva [a, *], R. Salsoso [a], T. Sáez [a], C. Sanhueza [a], F. Pardo [a], L. Sobrevia [a, b, c, *]

AIM OF THIS STUDY IS TO DETERMINE MATERNAL LIPID CONCENTRATION DURING PREGNANCY AND ESTABLISH THE TCh AND LDL PERCENTILES OVER WHICH FETOPLACENTAL ENDOTHELIAL DYSFUNCTION IS OBSERVED

.....Maternal TCh and LDL concentrations were inversely correlated with the maximal dilation, but the >75th percentile of maternal TCh and LDL concentrations (>291 and >169 mg/dL, respectively) correlated with reduced calcitonin gene-related peptide sensitivity of the vein rings.

Percentiles of maternal lipid concentration by trimester of pregnancy in the cross sectional lipids determination study.

	n	10th	25th	50th	75th	90th
TCh						
Pc	51	143	156	183	213	245
1st trimester	30	130	162	188	214	228
2nd trimester	41	182	205	234	275	280
3rd trimester	127	206	235	268	291	319
HDL						
Pc	51	45	53	58	71	90
1st trimester	30	47	57	66	76	86
2nd trimester	41	49	65	76	91	110
3rd trimester	127	53	64	75	83	99
LDL						
Pc	51	69	81	102	128	159
1st trimester	30	58	81	113	123	154
2nd trimester	41	86	102	124	146	160
3rd trimester	127	94	114	141	169	189
vLDL						
Pc	51	8	12	15	30	39
1st trimester	30	10	13	19	26	34
2nd trimester	41	18	25	32	38	51
3rd trimester	127	33	40	51	67	77
Tg						
Pc	51	33	58	80	145	182
1st trimester	30	52	64	98	132	168
2nd trimester	41	109	124	163	203	253
3rd trimester	127	157	186	228	275	337



HoFH and pregnancy: outcomes

MOTHER

- EXACERBATION OF PRE-EXISTING CV LESIONS DUE TO EXTREMELY HIGH CHOLESTEROL LEVELS AND HEMODINAMIC STRESS DURING PREGNANCY AND AT DELIVERY.

- INCREASE OF MOTHER'S PREDISPOSITION TO DEVELOP PREMATURE CARDIOVASCULAR DISEASE AFTER MONTHS/ YEARS WITHOUT EFFECTIVE TREATMENT DURING PREGNANCY AND LACTATION.

HoFH and pregnancy: outcomes

FETUS/CHILD

- MATERNAL HYPERCHOLESTEROLEMIA PROMOTES THE FORMATION OF FATTY STREAKS IN HUMAN FETAL AORTAS AND LEADS TO AN INCREASED SUSCEPTIBILITY TO ATHEROSCLEROSIS LATER IN LIFE

- ATHEROGENIC PROGRAMMING OF ARTERIAL ENDOTHELIAL CELLS BY MATERNAL HYPERCHOLESTEROLEMIA

- HYPERCHOLESTEROLEMIA DURING PREGNANCY INFLUENCES EPIGENETIC MODIFICATIONS AND LATER CARDIOVASCULAR DISEASE RISK IN OFFSPRING

NAPOLI C et Al. 1997,
PALINSKI W 2009,
BOGSRUD MP 2016

HoFH and pregnancy: management

CURRENT GUIDELINES RECOMMEND THAT ALL ADULT PATIENTS WITH FH RECEIVE LONG-TERM CHOLESTEROL-LOWERING THERAPY TO REDUCE LDL-C BY ≥ 50%. TO ACHIEVE THIS GOAL, THE USE OF A HIGH-DOSE STATIN IS REQUIRED.

THE TREATMENT OF FH BECOMES CHALLENGING IN **FEMALE PATIENTS WHO HAVE BECOME OR WISH TO BECOME PREGNANT** BECAUSE CHOLESTEROL LEVELS OFTEN INCREASE DURING PREGNANCY AND STATINS, AS A CLASS, ARE CONTRAINDICATED (CATEGORY X) DURING PREGNANCY AND LACTATION.

Eapen DJ et Al.Journal of Clinical Lipidology 2012

FH WOMEN AND FERTILITY: NICE GUIDANCE

Table 1. *Summary of NICE guidance on the management of fertility in women with familial hypercholesterolaemia*[4]

Period: prior to attempting to conceive

- When lipid-lowering medication is first considered for girls and women of childbearing age, risks to the pregnancy and the foetus while taking lipid-lowering medication should be discussed.
- Combined oral contraceptives are not generally contraindicated for women being treated with lipid-lowering therapy.

Period: attempting to conceive and during gestation

- There is no contraindication to pregnancy for the majority of women with FH.
- Women wishing to become pregnant should be advised to stop use of statins three months prior to attempting to conceive.
- Women with FH who are considering pregnancy or who are pregnant should be provided with shared care including expertise in both cardiology and obstetrics.
- In the unusual situation where a woman has symptoms of CHD or homozygous FH and is intending to become pregnant, she should discuss her intentions with her cardiologist.
- Women with FH who conceive while taking statins or other systemically absorbed lipid-lowering medications should be advised to stop treatment immediately and be referred to an obstetrician for foetal assessment.
- It is not useful to regularly measure cholesterol concentrations during pregnancy.

Period: lactation

- Women with FH should be encouraged to initiate breast-feeding. Only resins should be considered as lipid-lowering therapy during lactation.

FH = familial hypercholesterolaemia; CHD = coronary heart disease.

NHS
National Institute for Health and Clinical Excellence

BJOG 2009

HoFH and pregnancy : management

THE USE OF *STATINS* IS CONTRAINDICATED DURING PREGNANCY. NEW DRUGS (MIPOMERSEN, LOMITAPIDE) ARE NOT RECOMMENDED

Table 2 Lipid-lowering agents and pregnancy class

Lipid-lowering agents	Pregnancy class
Statins	X
Fibrates	C
Ezetimibe	C
Nicotinic acid	C
Cholestyramine	C
Colesevelam	B

THE ONLY MEDICATIONS CURRENTLY ACCEPTABLE TO USE DURING PREGNANCY ARE THE BILE ACID-BINDING RESINS, CHOLESTYRAMINE AND COLESEVELAM, BECAUSE THESE MEDICATIONS DO NOT PASS INTO THE SYSTEMIC CIRCULATION AND HAVE NOT BEEN SHOWN TO HAVE ANY ADVERSE EFFECTS

Table 2. *Lipid-lowering drugs around pregnancy*

	Approved	Contraindicated
Preconceptional phase (<3 months before stopping contraceptives)	Colestyramine (12-16 g OD, max. 24 g daily) Vitamin supplementation MgO_2 in case of constipation Colesevelam?	Statins Fibrates Ezetimibe Nicotinic acid
During pregnancy	Idem	Idem
Lactation period	Idem	Idem

EAPEN 2012

HoFH and pregnancy : *Low- Density Lipoprotein Apheresis*

LDL Apheresis in HoFH in pregnancy: indications

- CONTROINDICATION TO OTHER EFFECTIVE TREATMENTS AND THE ABSOLUTE NEED TO REDUCE THE MATERNAL LEVELS OF TC AND LDL-C
- REDUCE THE RISK OF FATAL WORSENING OF MATERNAL CV DISEASE
- REDUCE THE RISK OF PLACENTAL INSUFFICIENCY AND PREECLAMPSIA
- REDUCE THE RISK OF FETAL HYPERCHOLESTEROLEMIA

Atherosclerosis 254 (2016) 179–183

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Lipoprotein apheresis is essential for managing pregnancies in patients with homozygous familial hypercholesterolemia: Seven case series and discussion

Masatsune Ogura [a, *], Hisashi Makino [b], Chizuko Kamiya [c], Jun Yoshimatsu [c], Handrean Soran [d], Ruth Eatough [d], Giuseppina Perrone [e], Mariko Harada-Shiba [a], Claudia Stefanutti [f]

CASE SERIES

- 7 HoFH WOMEN
- 10 SUCCESSFUL DELIVERIES

ADVERSE EVENTS

PATIENTS 1 AND 2 DIED OF ACUTE MI DURING THE 3RD PREGNANCY AND 2 YEARS AFTER DELIVERY RESPECTIVELY. **THEY HAD BOTH REFUSED TO UNDERGO LA DURING PREGNANCY**

RESULTS:

- **MOST PATIENTS WERE CAPABLE OF GIVING BIRTH SUCCESSFULLY AND NO BABIES SHOWED ANY ANOMALIES OR IUGR..**
- **WE OBSERVED REPEATED PREGNANCIES IN 4 PATIENTS WHO RECEIVED LA DURING PREVIOUS PREGNANCY.**

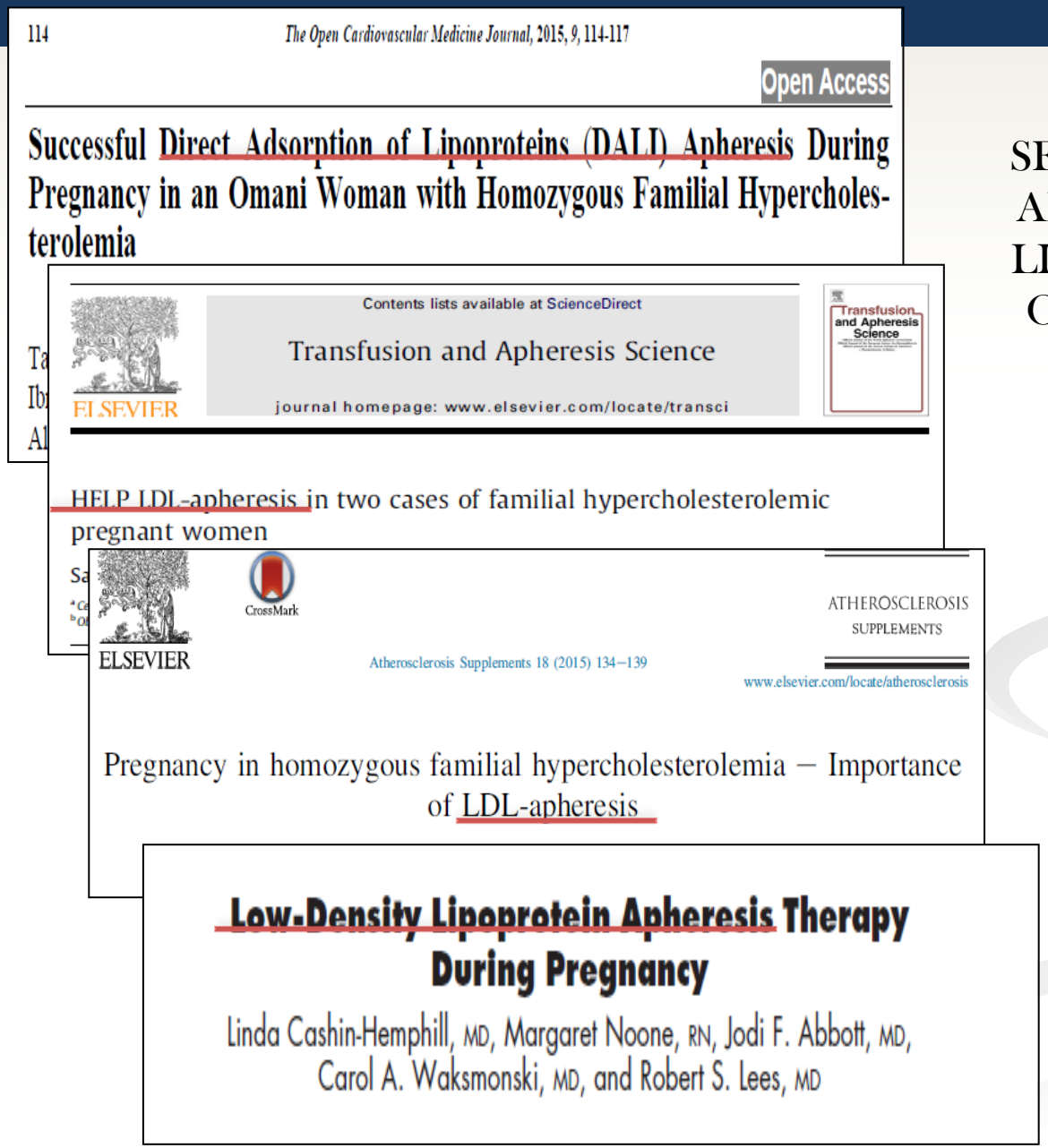
LIPOPROTEIN APHERESIS IS ESSENTIAL FOR MANAGING PREGNANCIES SAFELY IN PATIENTS WITH HoFH.

PATIENTS DATA

	Adherence to LA	Pregnancy outcomes	Neonatal outcome	Patient follow up
Case 1	Poor	1st: vaginal delivery 2nd: vaginal delivery 3rd: miscarriage at 20 weeks	**Normal at term** **Normal at term**	deceased
Case 2	Poor	Caesarean section	**Normal at term**	deceased
Case 3	Good	1st: abortion 2nd: Caesarean section (maternal angina)	**Normal preterm**	alive
Case 4	Good	1st: Caesarean section 2nd: Caesarean section	**Normal at term** **Normal at term**	alive
Case 5	Good	Caesarean section	**Normal at term**	alive
Case 6	Good	1st: Caesarean section 2nd: Caesarean section (placenta previa)	**Normal at term** **Normal preterm**	alive
Case 7	Good	vaginal delivery	**Normal at term**	alive

Ogura 2016

HoFH AND PREGNANCY: STATE OF ART



114 *The Open Cardiovascular Medicine Journal*, 2015, 9, 114-117

Open Access

Successful Direct Adsorption of Lipoproteins (DALI) Apheresis During Pregnancy in an Omani Woman with Homozygous Familial Hypercholesterolemia

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

HELP LDL-apheresis in two cases of familial hypercholesterolemic pregnant women

ELSEVIER

Atherosclerosis Supplements 18 (2015) 134–139

ATHEROSCLEROSIS SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

Pregnancy in homozygous familial hypercholesterolemia – Importance of LDL-apheresis

Low-Density Lipoprotein Apheresis Therapy During Pregnancy

Linda Cashin-Hemphill, MD, Margaret Noone, RN, Jodi F. Abbott, MD, Carol A. Waksmonski, MD, and Robert S. Lees, MD

SEVERAL DIFFERENT KINDS OF APHERESIS ARE DESCRIBED IN LITERATURE FOR TREATMENT OF HoFH PREGNANT WOMEN

- DIRECT ADSORBIPTION OF LIPOPROTEIN APHERESIS (DALI)
- HEPARIN EXTRACORPOREAL LDL-C PRECIPITATION (HELP) APHERESIS
- CASCADE FILTRATION SYSTEM APHERESIS
- LOW DENSITY LIPOPROTEIN APHERESIS

HoFH AND PREGNANCY: APHERESIS

- LITERATURE REVIEWS FOCUSED ON HoFH WOMEN TREATED WITH APHERESIS DURING PREGNANCY

1997-2017

7 ARTICLES
- 5 CASE REPORTS
- 2 CASE SERIES

↓

- 14 PATIENTS
- 22 PREGNANCIES

↓

- 1 EARLY MISCARRIAGE
- 1 LATE ABORTION
- 1 ELECTIVE PREGNANCY TERMINATION BECAUSE OF WORSENING MATERNAL CONDITIONS
- 2 PRETERM DELIVERIES FOR MATERNAL INDICATION
- 1 PRETERM DELIVERY FOR OBSTETRIC CONDITION (PLACENTA PREVIA)
- 16 FULL TERM DELIVERIES

LDL-APHERESIS IN HoFH PREGNANT PATIENTS

	CV STATE	N. CICLES	TYPE OF APHERESIS	OBSTETRIC COMPLICATIONS	DELIVERY	NEWBORN
BEIGEL 1998	2 CAD	BIWEEKLY 1	PEX PEX	NO SYNCOPE	4 FULLTERM DELIVERIES EPT AT 18 WEEKS	ALL NEWBORNS WERE HEALTHY
CASHIN-HEMPHILL 2000	PREVIOUS INFERIOR AMI	8	HELP	NO	FULLTERM VD	HEALTHY 3098 GR
ERTORER 2008	HEALTHY	12	CF	NO	FULLTERM CS	HEALTHY 3100 GR
ANEDDA 2011	PREMARURE CORONARY DISEASE	22	HELP	HYPERTENSION	PRETERM CS 34 WS	HEALTHY 2100 GR
AL-DUGHAISHI 2015	MODESTE AORTIC STENOSIS	12	DALI	NO	FULLTERM VD	HEALTHY 2100 GR
BLAHA 2015	ATHEROSCLEROTIC AORTAL PLAQUE	NP	LA	NO	FULLTERM VD	HEALTHY 2890 GR
OGURA 2016	2 HEALTHY 4 CAD 1 OLD AMI	WEEKLY BIWEEKLY	PEX DFPP DSA	NO	8 FULLTERM DELIVERIES 2 PRETERM DELIVERIES	ALL NEWBORNS WERE HEALTHY

C.F.: LIPOPROTEIN APHERESIS WITH CASCADE FILTRATION; C.S.: CESAREAN SECTION; V.D.: VAGINAL DELIVERY; AMI: ACUTE MYOCARDIAL INFARTION; HELP: HEPARIN-INDUCED EXTRACORPOREAL LIPOPROTEIN PRECIPITATION APHERESIS; DALI: DIRECT ASSORBITION OF LIPOPROTEIN APHERESIS; NP: NOT PRECISED; L.A. LIPOPROTEIN APHERESIS;CAD: CORONARY AORTIC DISEASE; DFPP, DOUBLE FILTRATION PLASMAPHERESIS; DSA, DEXTRAN-SULFATE ABSORPTION; EPT: ELECTIVE TERMINATION OF PREGNANCY

LDL Apheresis in HoFH in pregnancy: management

- PRE CONCEPTION COUNSELLING : EVALUATION OF CV CONDITIONS, DISCONTINUATION OF STATIN, LDL APHERESIS INDICATIONS IN PREGNANCY
- PREGNANCY CARE AT SPECIALIZED CENTER (IUGR AND PE RISK)
- MANAGEMENT OF DELIVERY
- BREAST FEEDING
- MATERNAL FOLLOW-UP BEFORE AND POST PREGNANCY
- POST PARTUM CONTRACEPTION
- NEWBORN FOLLOW UP

Pregnancy in HoFH patients: conclusions

APPROACHING A HoFH PREGNANT WOMAN WE HAVE TO:

- COUNSEL THE PATIENT ABOUT THE SEVERITY OF HER CONDITION IN PREGNANCY AND ABOUT POOR PROGNOSIS IN NOT-TREATED PATIENTS
- INFORM THE PATIENT THAT ALMOST ALL CASES OF HoFH PREGNANCIES TREATED WITH APHERESIS ENDED WITH FULL TERM DELIVERIES
- PROPOSE APHERESIS FROM THE FIRST TRIMESTER AS A THERAPY SAFE FOR MOTHER AND FETUS (CONTROINDICATION OF STATIN)
- FOLLOW THIS PATIENT CLOSELY IN A TERTIARY CARE CENTER WITH A MULTIDISCIPLINARY MEDICAL TEAM

HoFH AND PREGNANCY: FUTURE PERSPECTIVES

- SPECIFIC GUIDELINES ABOUT THE USE OF THERAPEUTIC APHERESIS IN THESE PATIENTS

- ORGANIZATION OF MEDICAL TEAMS DEDICATED TO THESE PATIENTS

- NEW DRUGS

- SPECIFIC ITEMS OF SURVEILLANCE IN PATIENTS WHO REFUSE APHERESIS

THANK YOU FOR YOUR ATTENTION