

Pregnancies in Women With Long-Chain Fatty Acid Oxidation Disorders

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European
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Pregnancies in women with long-chain fatty acid oxidation disorders

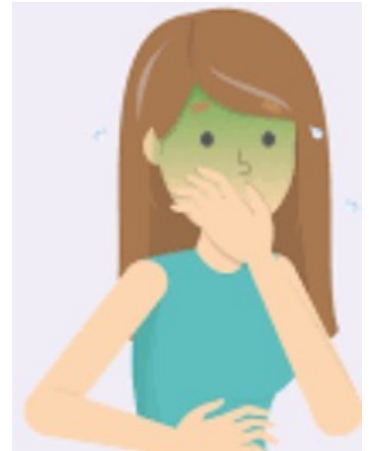
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Background

- With improvement in diagnostics and treatment (NBS), an increasing number of women with lcFAODs are reaching child-bearing age and planning pregnancy.
- Pregnancy may increase the risk of acute metabolic decompensation due to catabolism and/or increased metabolic demand in women with lcFAODs.
- Triggers of catabolism in pregnancy:
 - nausea or vomiting with decreased energy intake (1. trimester)
 - increasing energy demand of the growing foetus (from 2. trimester)
 - peripartum changes
 - breastfeeding



Phases of gestation

- complex endocrine-metabolic rearrangement
- First phase of gestation: "maternal anabolic phase"
 - increase in maternal energy reserves, mainly in the form of lipids, storing the substrates to meet the maternal-foetal needs of advanced gestation and breastfeeding
- Second phase: "maternal catabolic phase" or "foetal anabolic phase"
 - aims to promote foetal growth
 - reduced insulin sensitivity => increase in maternal concentrations of glucose and free fatty acids



What is known...

- Most patients with IcFAODs are diagnosed before pregnancy
- Individuals with the myopathic form of CPT2 deficiency can remain asymptomatic until adulthood, and pregnancy can be the first trigger that leads to a decompensation with rhabdomyolysis
- Reports of asymptomatic affected women during pregnancy and delivery identified due to an abnormal newborn screen in their healthy child
- To date, information on the management and outcome of pregnancies is scarce and limited to few case reports, mainly of VLCAD and CPT2 deficiencies

International survey study

Two parts:

- 1) Patient-specific data on pregnancy courses and outcomes
- 2) Data on management of IcFAOD pregnancies
Including colleagues that have not yet treated pregnant IcFAOD patients but are involved in the care of these patients

Aim of the study and methods: Part 1

- Collection of data on management and outcomes of pregnancies in IcFAODs via an international questionnaire-based survey among metabolic centres
- Survey: 36 questions addressing
 - patient history
 - the number and outcome of pregnancies
 - pregnancy course and complications
 - dietary management during pregnancy
 - management of delivery
 - peripartum complications
 - breast-feeding



Survey

- Survey developed by paediatric and adult metabolic specialists from 6 metabolic centres that had experience in the management of pregnancies with IcFAODs
- sent out in December 2024 to expert healthcare professionals, including
 - 1) all members of the C-FAO subnetwork of MetabERN
 - 2) members of the international guideline group for IcFAODs
 - 3) members of INFORM Network
 - 4) additional colleagues who were known to the authors to be involved in the care of patients with IcFAODs

International survey study



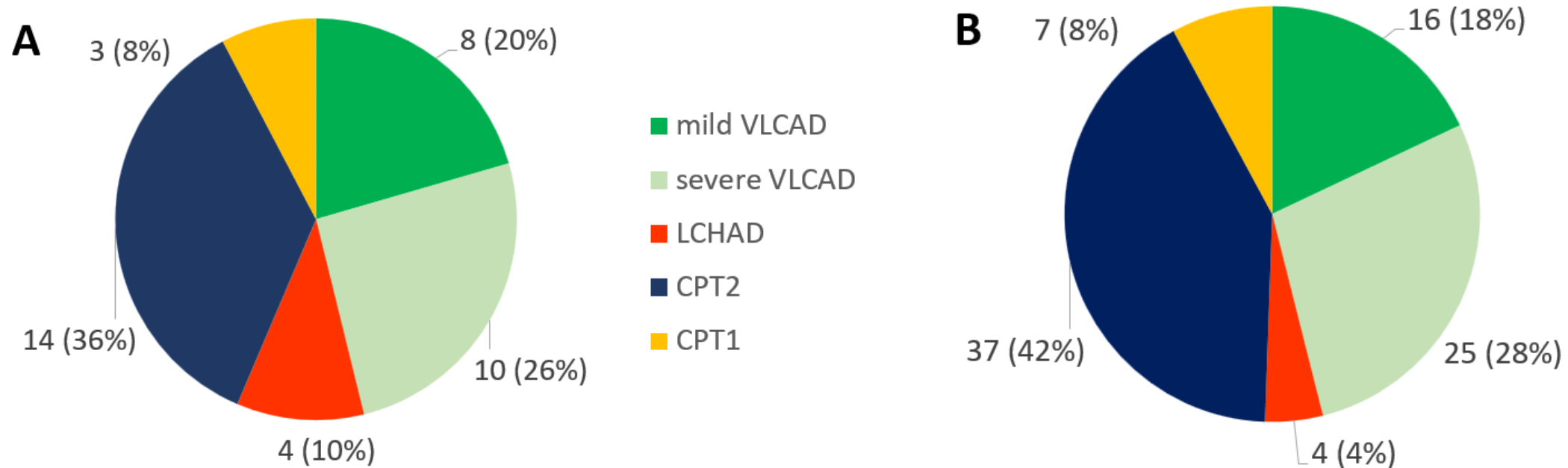
ORIGINAL ARTICLE | Open Access |

Pregnancies in Women With Long-Chain Fatty Acid Oxidation Disorders: Results of a European and North American Survey

[Sarah C. Grünert](#) , [Mirjam Langeveld](#), [Lisa Rudolph](#), [Ute Spiekerkoetter](#), [Allan M. Lund](#), [Annalisa Sechi](#), [Halil Tuna Akar](#), [Karolina M. Stepien](#), [Hanım Aghakishili](#), [Amelie S. Lotz-Havla](#) ... [See all authors](#) ▾

- 89 pregnancies reported in 39 women
- managed by 22 metabolic centres worldwide

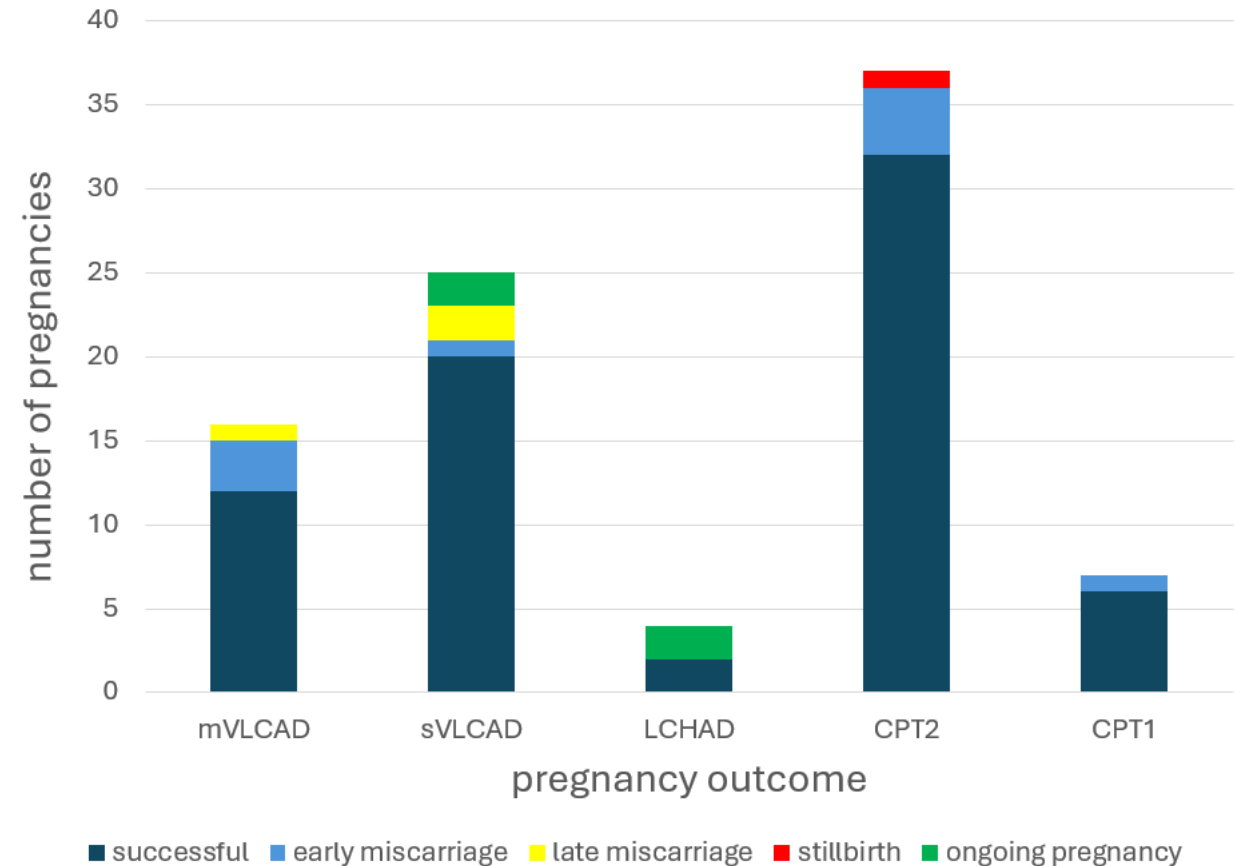
Patient cohort and pregnancies



A) Distribution of disorders among 39 women with lcFAODs in this study. (B) Numbers of pregnancies per disease type (lcFAOD) and percentage of the total pregnancy number of 89 in this cohort.

Pregnancy outcomes

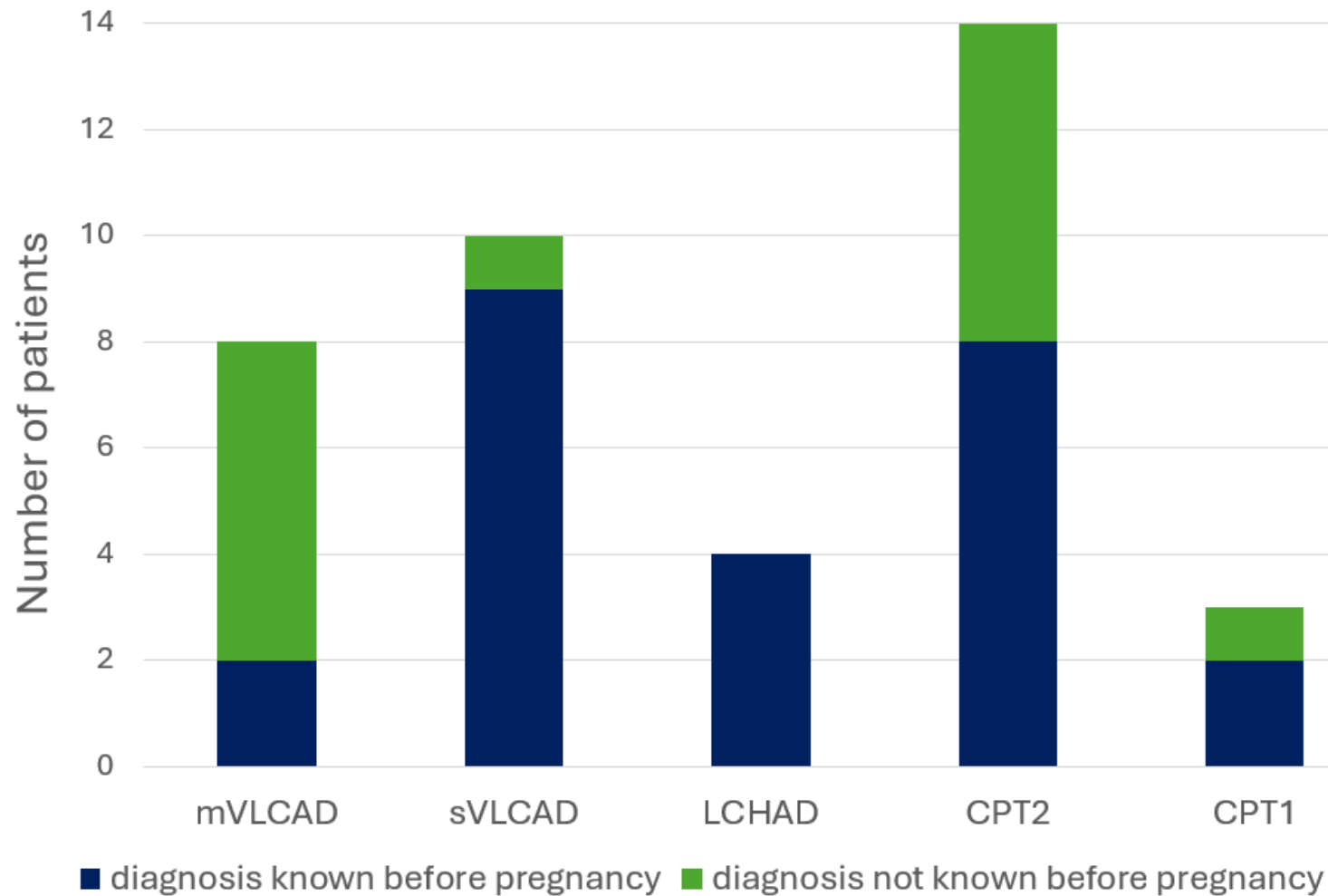
- 72 live births
- 9 early miscarriage (< 12 weeks of gestation)
- 3 in late miscarriage (> 12 weeks of gestation)
- one in stillbirth at 41 weeks of gestation
- 4 women were still pregnant (first trimester, 15th, 24th, and 30th week of gestation) at the time of the survey



Diagnosis and symptoms before pregnancy

- None of the patients diagnosed by newborn screening
- In most patients, the diagnosis was made after symptomatic presentation with onset of symptoms between childhood and adulthood
- 30/38 patients symptomatic before pregnancy (78.9%)
- 8/38 women asymptomatic before pregnancy (21.1%)
- Diagnosis known before the first pregnancy in 25/39 women (64.1%), whereas 14 women had at least one pregnancy before diagnosis (14/39; 35.9%)
- No woman, in whom the diagnosis was made because of pregnancy induced symptoms

Diagnosis before pregnancy

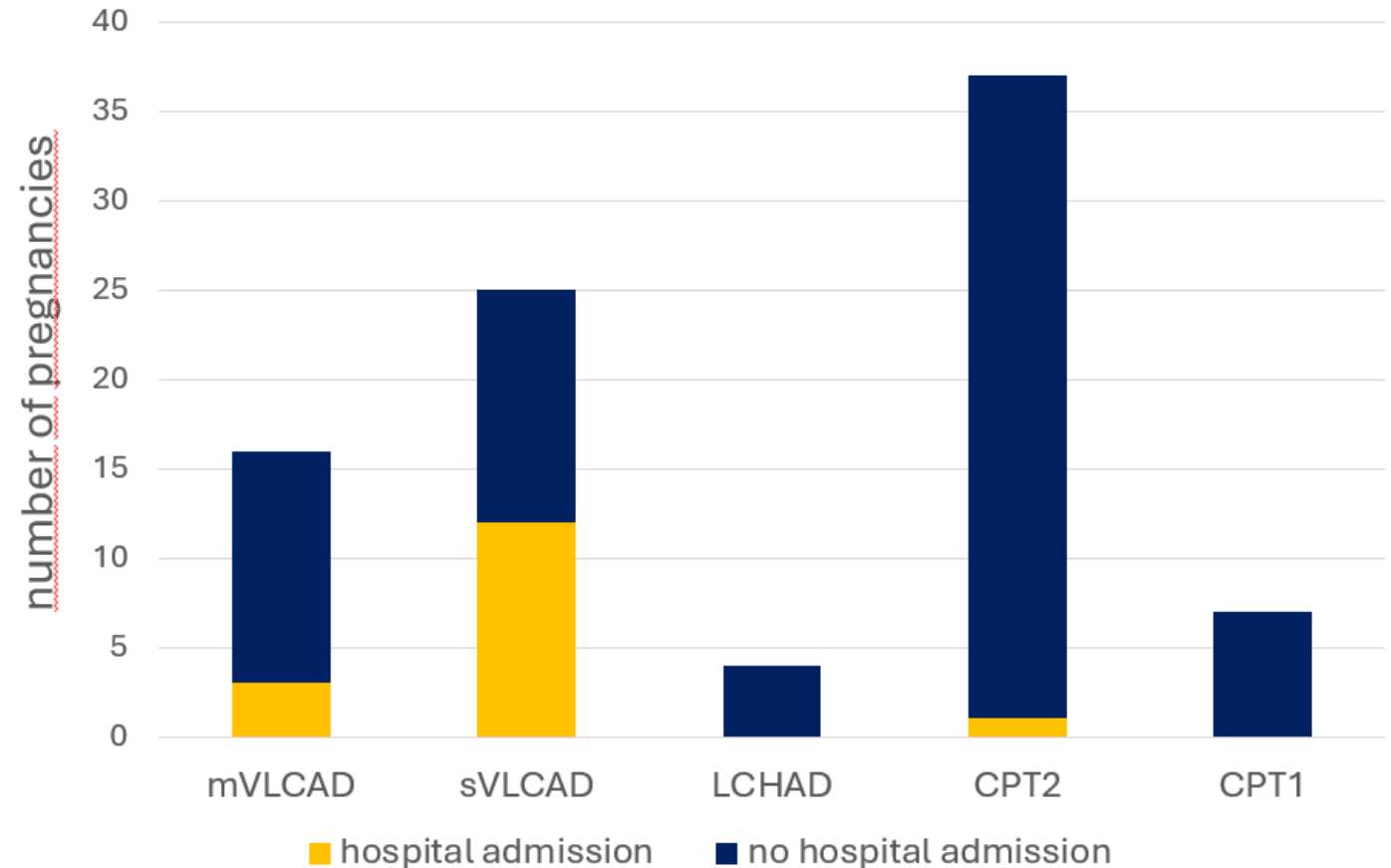


Diagnosis and symptoms before pregnancy

- One patient was diagnosed at 10 weeks of gestation
- One woman at age 32 years following metabolic decompensation after giving birth to her second child
- In one woman with 6 pregnancies, the diagnosis was established between the 5th and 6th pregnancy.
- One patient who had experienced muscular symptoms at school age was diagnosed in adulthood after her son had been diagnosed with CPT2 deficiency by selective screening.
- The latest diagnosis was made in a 75-year-old woman with 5 successful pregnancies, when she presented to hospital with rhabdomyolysis following a febrile illness. However, she had experienced myalgia and difficulties walking after all 5 deliveries and remembered that she had dark urine during these episodes.

Course of pregnancy and metabolic stability

- Age at first pregnancy 18 to 38 years (median 28 years)
- Data on hospital admissions are available for 83 pregnancies.
- During 16 pregnancies, women were admitted to hospital, up to a maximum of 4 times per pregnancy.

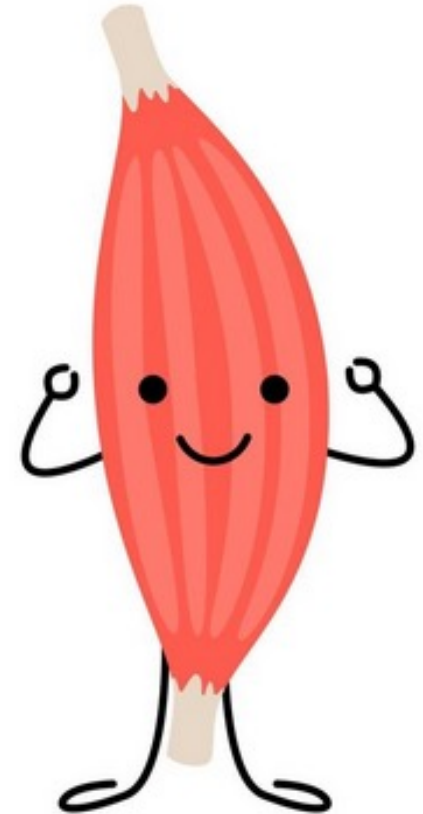


Course of pregnancy and metabolic stability

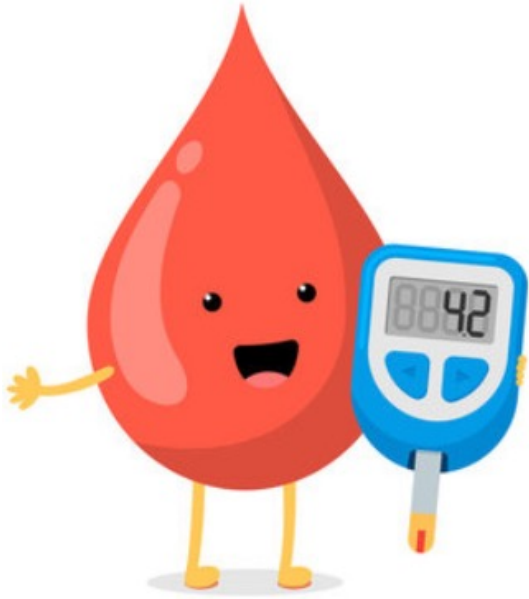
- Indications for hospital admissions rarely reported, but if mentioned included nausea, vomiting, poor calorie intake, infections, rhabdomyolysis, indigestion, and arterial hypertension.
- Seven out of 36 women (7/36; 19.4%) had at least one metabolic decompensation during pregnancy (mild VLCAD deficiency $n = 1$, severe VLCAD deficiency $n = 3$, CPT2 deficiency $n = 2$, CPT1 deficiency $n = 1$).
- In patients with muscular FAODS, these were usually associated with relevant creatine kinase (CK) elevation.

Muscular symptoms

- In 9 patients (24%), muscular symptoms recurred or worsened during pregnancy.
- In one patient, the muscular pain was so severe that she spent several weeks in bed and was unable to manage daily activities.
- None of the patients developed cardiomyopathy!
- One patient stated that she never felt better than during her pregnancies!



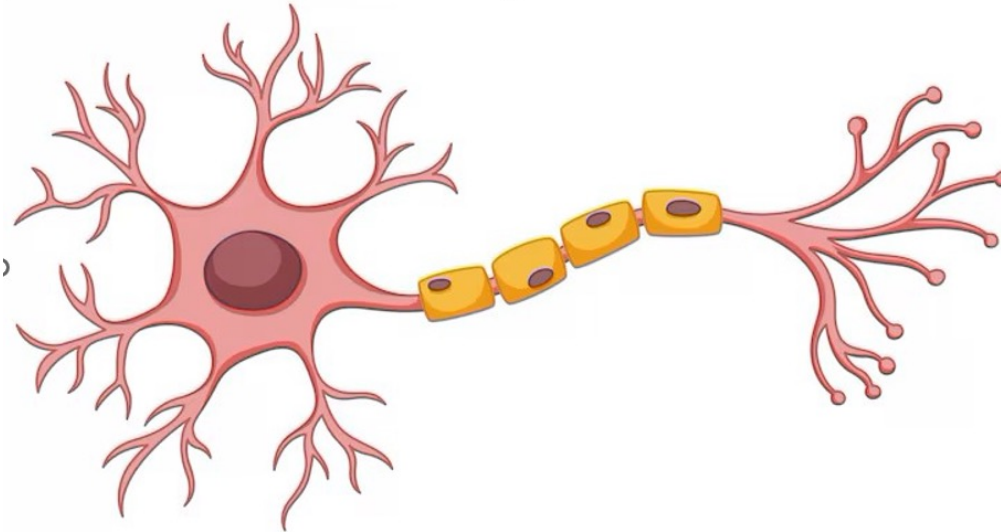
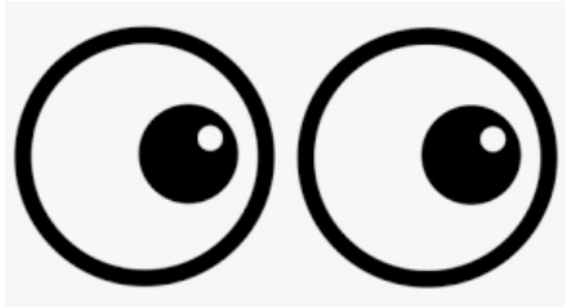
Hypoglycemia



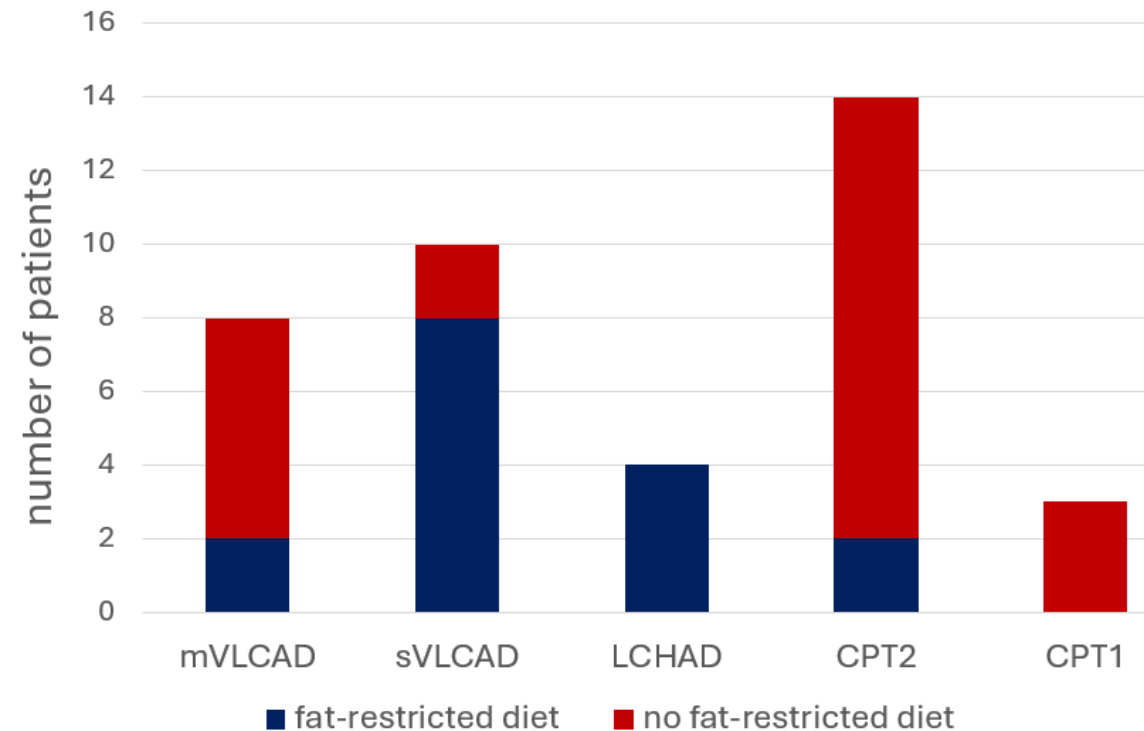
- Three women with severe VLCAD deficiency (3/38; 7.9%) suffered from aggravated hypoglycemia
- In one woman, this mainly occurred in the first trimester.
- One other patient was admitted four times due to dehydration and hypoglycemia.
- The third woman had a reduced fasting tolerance during pregnancy and required frequent meals in small portions.

Retinopathy and Neuropathy

- No deterioration of neuropathy and retinopathy was reported during pregnancy in patients with LCHAD deficiency.



Dietary and Medical treatment



- Only 16 patients were on a long-chain fat-restricted diet before their first pregnancy
- Three women were on a strict fat-reduced diet with $< 10\%$ of the total daily energy intake as LCT fat, while the others only had a moderate fat restriction.
- Only 3 women were advised a change in their dietary management during pregnancy.
- Enteral tube feeding during pregnancy was necessary to establish metabolic stability in one woman

Obstetric complications

- Data available on 67 successful pregnancies: 56 were unremarkable
- Obstetric complications in the remaining 11:
 - High blood pressure
 - Elevated liver enzymes
 - Placental insufficiency
 - Gestational diabetes
 - Infection etc.



Management of delivery

- Hospital delivery in 72/82 (88%)
- 28 in a hospital with metabolic expertise
- 20 in a local hospital with consultation with a metabolic expert from elsewhere
- 24 were managed in a local hospital without metabolic expertise (mainly due to unknown diagnosis)



Mode of delivery

- Known for 69 cases
 - Spontaneous vaginal delivery (28/69; 40.6%)
 - Induction of labor (23/69; 33.3%)
 - Elective Caesarean section (13/69; 18.8%)
 - Emergency Caesarean section (5/69; 7.2%)
-
- 94% of babies born at term
 - Four preterm babies
 - Most children were healthy (67/71; 94.4%), while 3 children initially needed NICU care, either due to prematurity or due to perinatal problems
 - One stillbirth (41 weeks, CPT2)



Delivery

- Most deliveries were uneventful
- Umbilical cord wrapping (n=2)
- Ventouse delivery (n=1)
- Fever during labor requiring antibiotics (n=1)
- Hysterectomy after delivery (n=1)
- One patient with preeclampsia and chorioamnionitis developed postpartum hemorrhage with tachycardia and an ileus
- The mother with CPT1 deficiency, who gave birth in the 28th week of pregnancy, required intensive care treatment with mechanical ventilation. She presented with edema, elevated liver enzymes, hyperbilirubinemia, and metabolic acidosis

Delivery management

- 50% of labors were managed with preventive i.v. glucose infusions.
- In 6 patients, an increased oral carbohydrate intake was additionally recommended.
- One woman with severe VLCAD deficiency additionally received i.v. amino acids, L-carnitine, and Dojolvi.
- Hypoglycemia in the offspring during the first days of life was reported in at least 3 babies, presumed due to the high glucose supply of the mother during labor
- In the remaining 35 labors, no special measures were taken, mainly because the diagnosis of the mother was not known at the time of delivery (35/70; 50%).



Newborn screening



- Abnormal newborn screening results were reported in the babies of 2 mothers with severe VLCAD deficiency
- Elevated metabolites in the initial screening sample, normalized on repeated testing.
- In one of them, daily dried blood spot samples were taken, and the maternal abnormal metabolites could be detected in the baby until day 4 of life.

Postpartal problems

- Metabolic decompensation within the postpartum period in 21%
- Between a few hours and up to 3 months after delivery
- In one woman who had a Caesarean section, the CK level increased up to 29 700 U/L at the 6th postoperative hour despite continuous i.v. glucose infusion during surgery and postpartum (asymptomatic).
- One patient with CPT2 deficiency diagnosed at age 75 years gave birth at home to 5 healthy sons and reported that she had myalgia after all 5 deliveries, difficulties walking, dark urine. Admitted to hospital on two of these occasions a few days after delivery

Breastfeeding

- Information on breast-feeding is available for 58 babies
- 38 were breast-fed (66%) (4 mVLCAD, 13 sVLCAD, 21 CPT2)
- Only four women were recommended a higher energy intake during lactation, and two of them an increase in MCT



Conclusions

- Mainly patients with VLCAD and CPT2 deficiencies
- Our report on successful pregnancies LCHAD and CPT1 deficiency provides more information on the pregnancy experience of the more severe phenotypes of lcFAODs
- The majority of pregnancies in women with lcFAODs result in the delivery of a healthy baby
- Approximately 20% of women experience metabolic decompensations during pregnancy and/or in the postpartum period
- Good counseling of patients before pregnancy necessary!
- Most women maintained stable metabolic states throughout gestation, often even in the absence of strict dietary treatment (especially mVLCAD and CPT2)

Conclusions

- Need for a personalized approach with evaluation of the necessity and intensity of dietary interventions, dependent on the patient's previous history and clinical severity of the enzymatic defect
- Only one woman in this study used triheptanoin during pregnancy
- Pregnancy courses highly variable in patients with same metabolic defect
- Some patients report metabolic stabilization
- No maternal deaths



Never felt better than during my three pregnancies"

Conclusions

- No patients with deterioration of cardiomyopathy during pregnancy or postpartum, but one case report in the literature (Murata et al.)
- Metabolic decompensations more common after spontaneous vaginal delivery or induced labor compared to Caesarean section; however, we cannot conclusively recommend any specific mode of delivery from our data
- Most women were able to breastfeed their child, and no metabolic decompensations clearly triggered by lactation were reported

Limitations



- Selection bias: I.e. the rate of successful pregnancies must be interpreted with caution as there might be underreporting of unsuccessful (or successful) pregnancies or miscarriages that the treating physicians might not have been aware of
- Detailed information was not available for all pregnancies as some of them occurred decades ago.



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Part 2

Toward Standardized Care: International Expert Survey on Pregnancy Management in Long-Chain Fatty Acid Oxidation Disorders and Unmet Needs

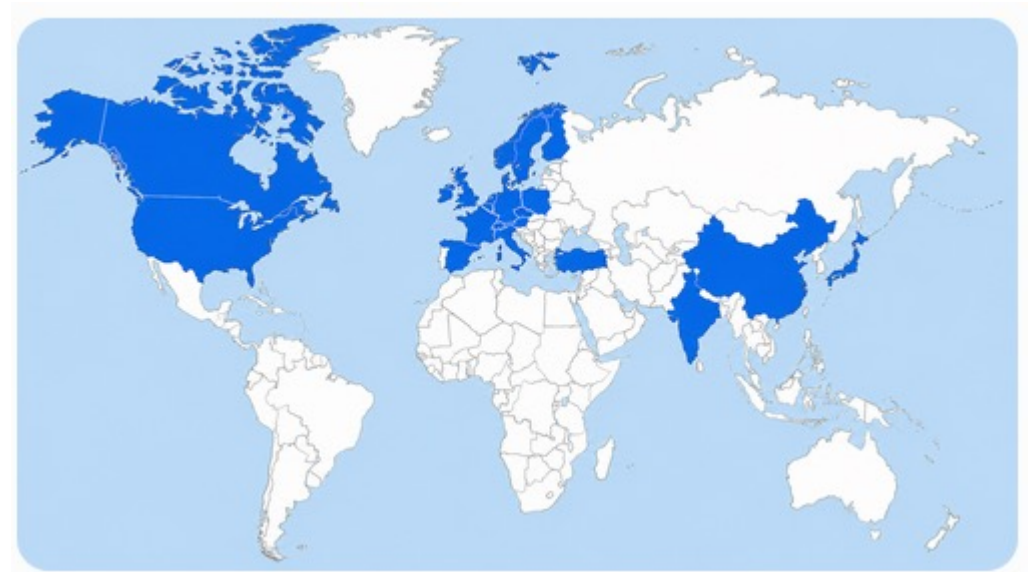
Aim of the study and methods: Part 2

- Collection of data on management of IcFAOD pregnancies among metabolic centres (web-based survey)
 - Preconception counseling
 - Pregnancy follow-up and monitoring
 - Peri- and postpartum management
 - Lactation
 - Assessment of metabolic stability
 - Emergency preparedness

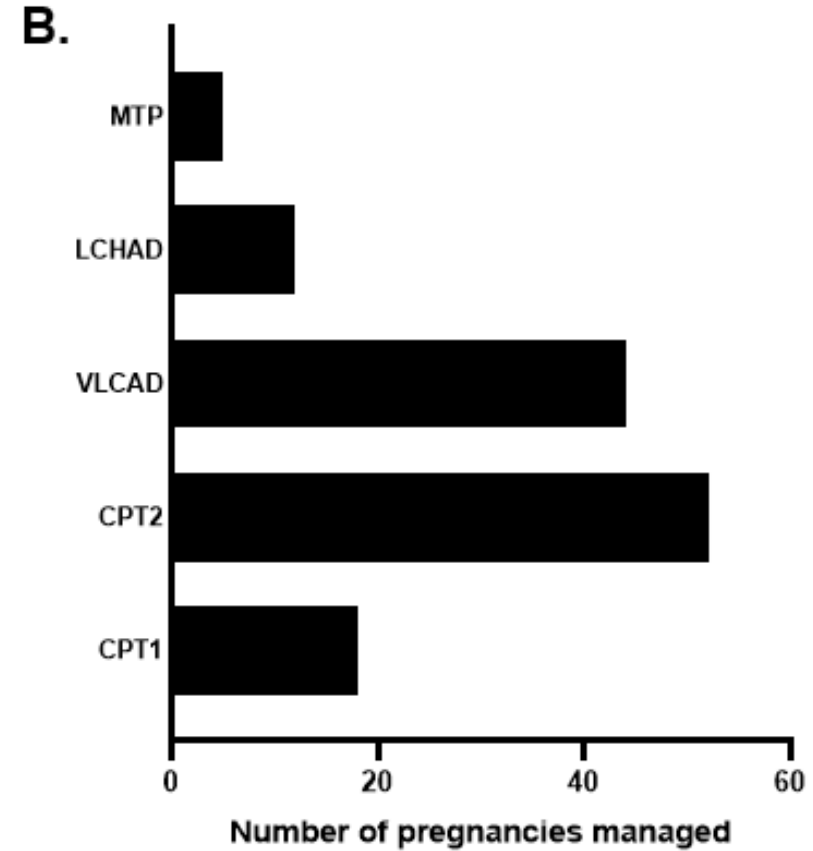
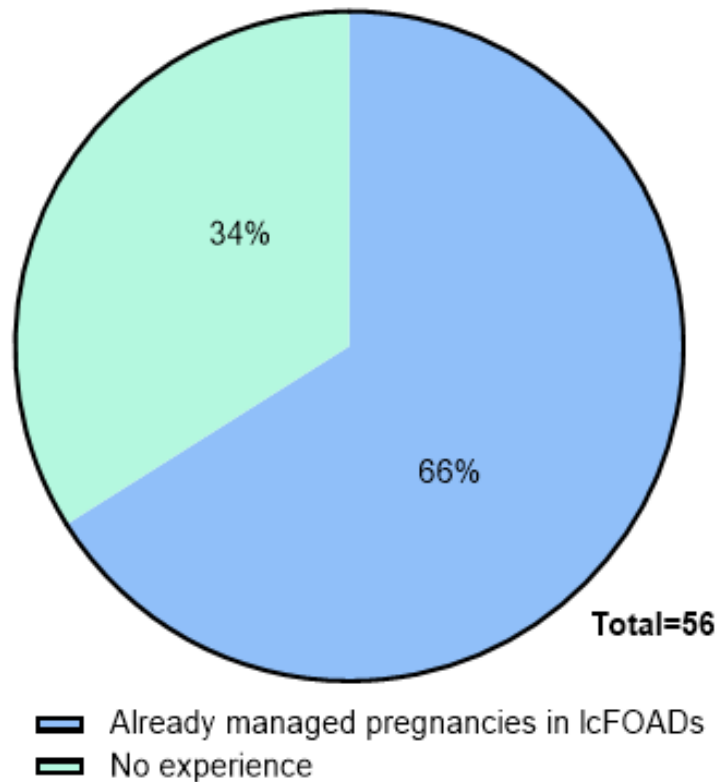


International survey study

- Same expert healthcare professionals as first survey (n=24)
- Additional colleagues/metabolic centres that have not yet treated pregnant IcFAOD patients but are involved in the care of these patients (n=31)
- 55 metabolic centers from 21 countries in Europe, North America and Asia
- Mainly metabolic pediatricians (65%) and adult metabolic physicians (41%)



Experience of participants



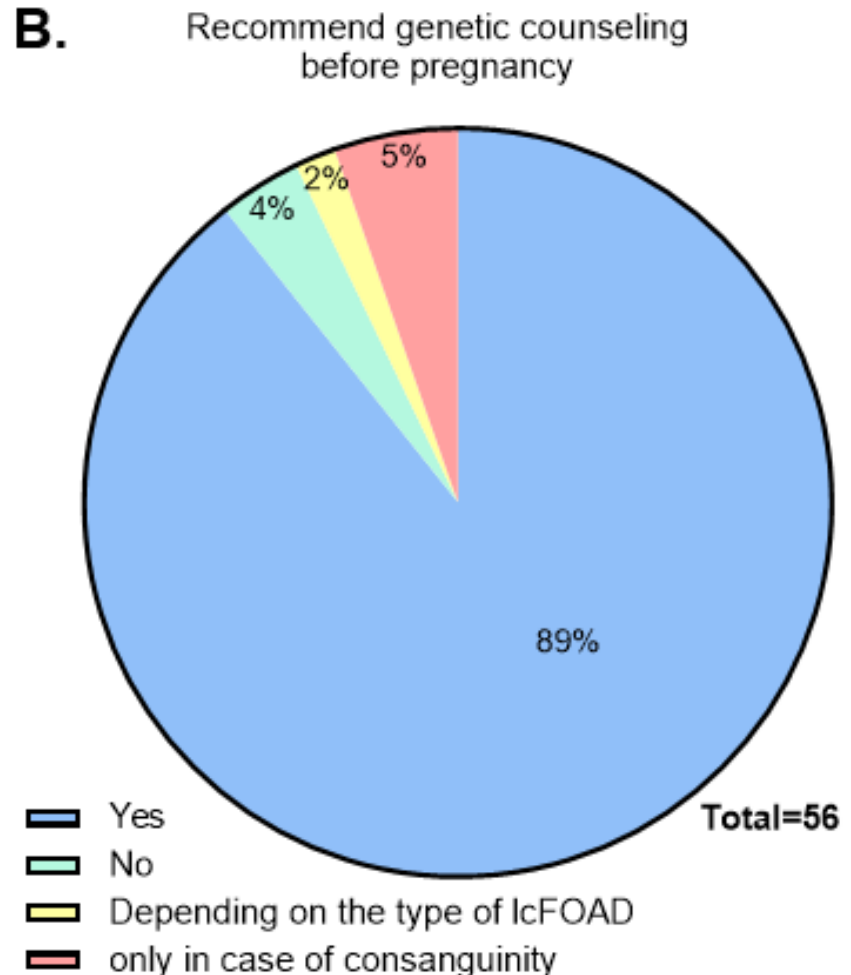
n=131

Preconception counseling

- 91% of respondents indicated that they routinely and proactively inquire about a potential wish for pregnancy in women of reproductive age with lCFAODs
- Counseling typically included
 - discussion of maternal metabolic risks
 - the importance of achieving stable metabolic control prior to conception
 - optimization of nutritional status
 - advance planning of multidisciplinary care during pregnancy

Encouragement of planned pregnancies to ensure coordinated metabolic and obstetric management

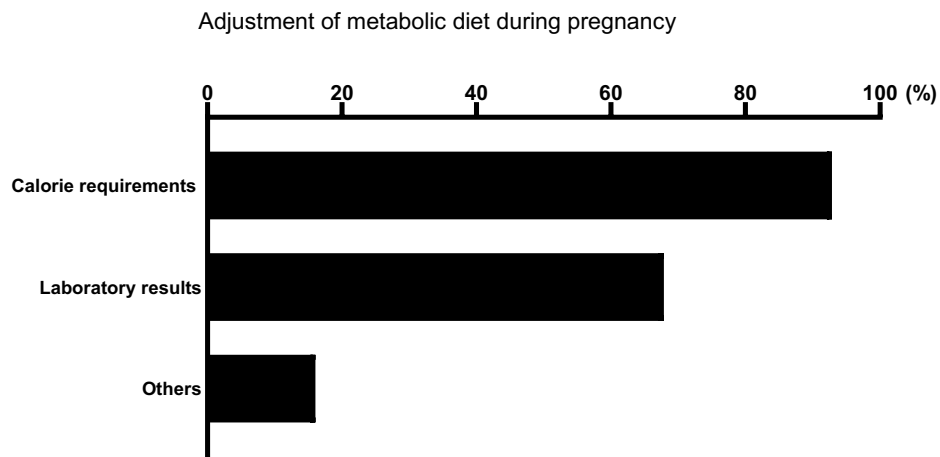
Genetic counseling



- Recommended by most doctors
- Especially in CPT2, pregnancies before diagnosis of the FAOD were common

Dietary adjustments during pregnancy

Management highly individualized!

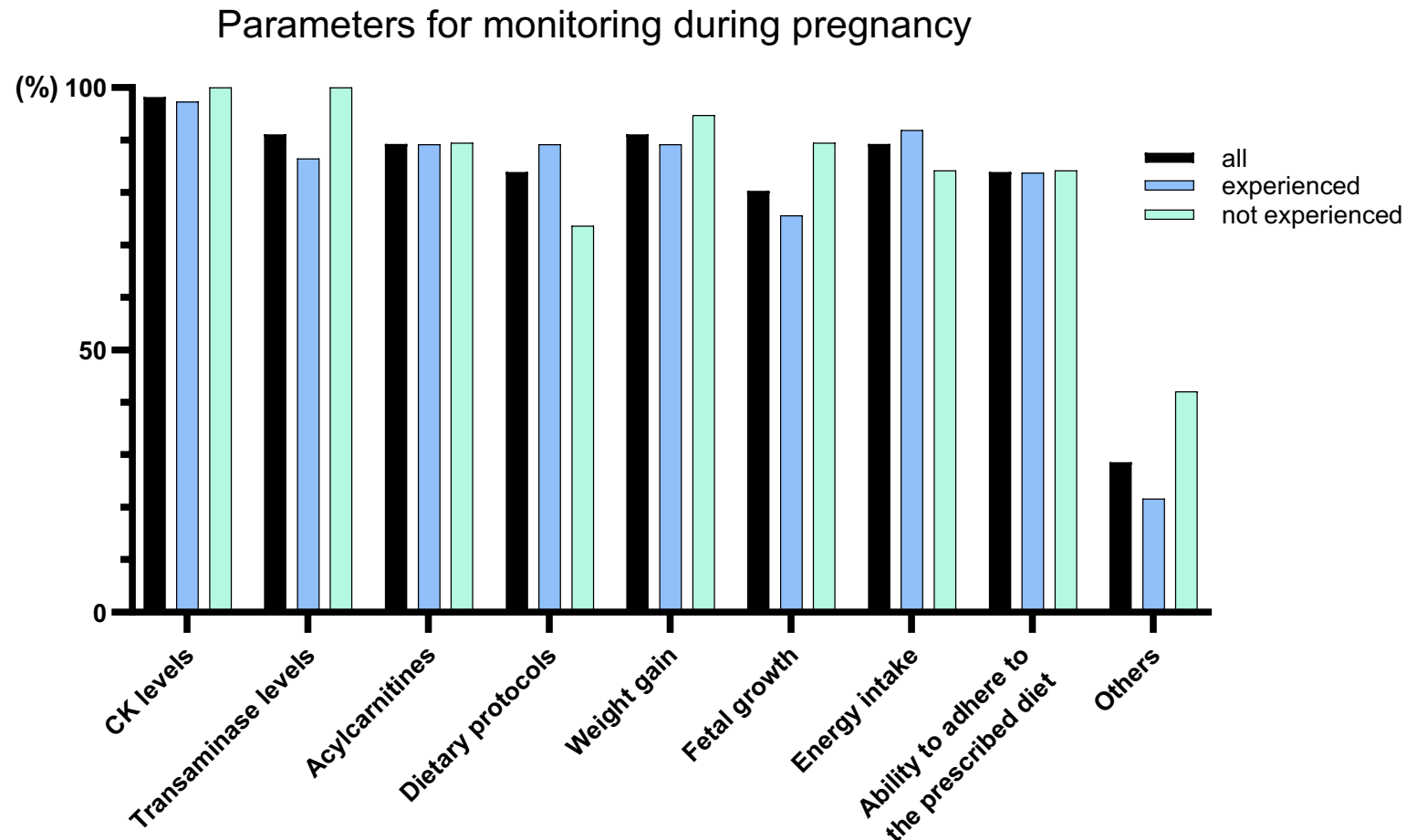


Dietary adjustments tailored to

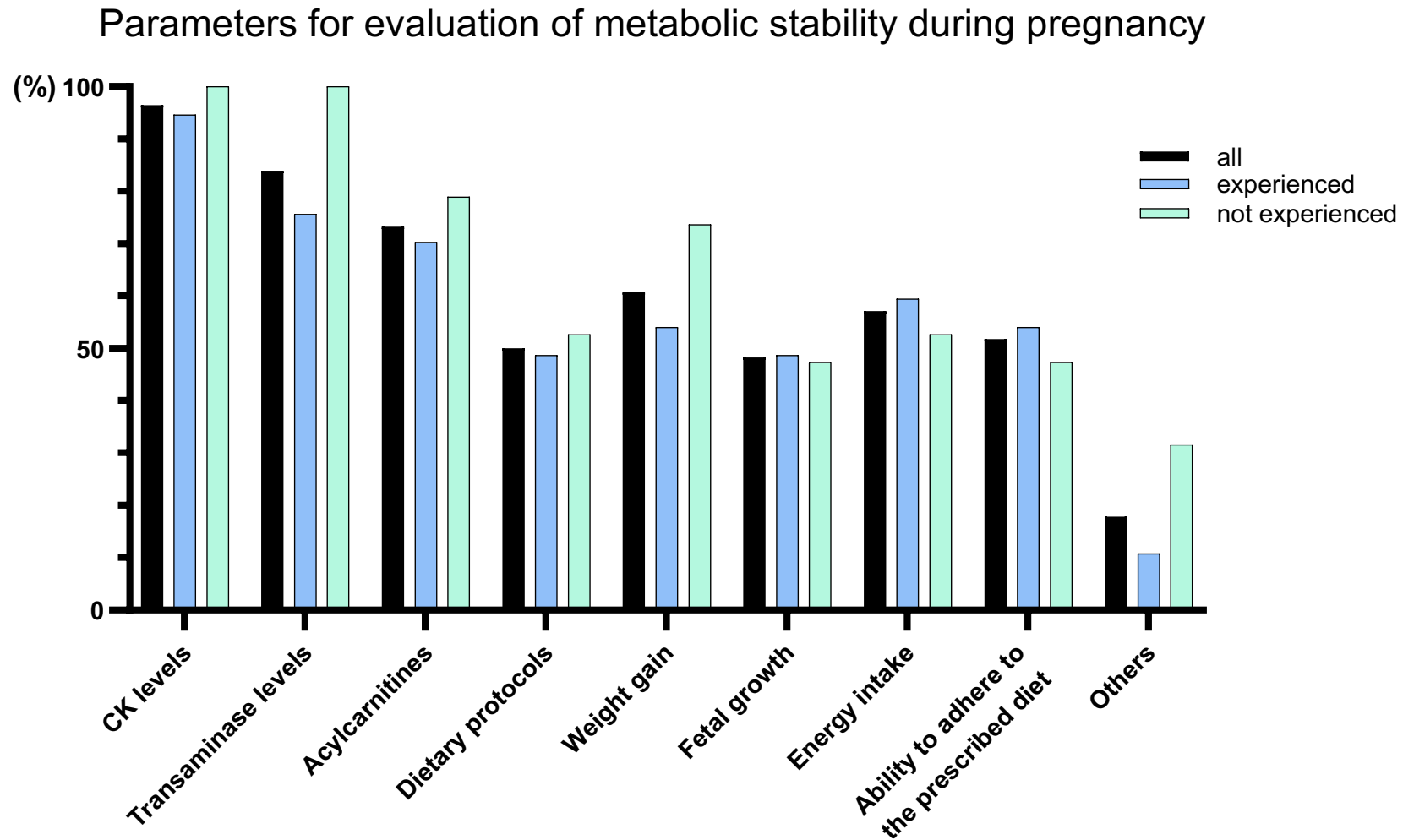
- maternal symptoms
- fasting tolerance
- oral intake (particularly during hyperemesis)
- weight gain
- fetal growth

Monitoring parameters

Multimodal approach



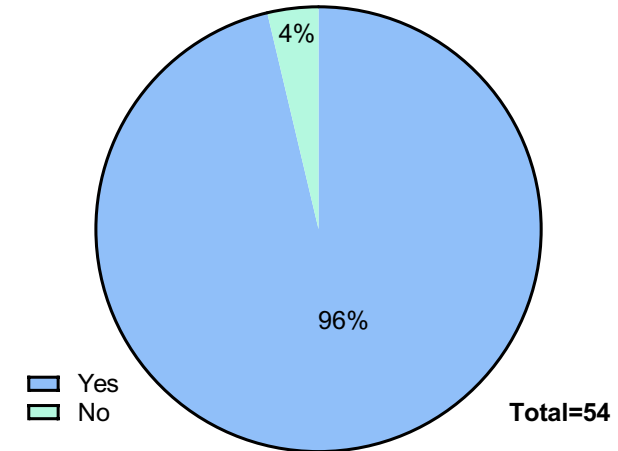
Assessment of metabolic stability



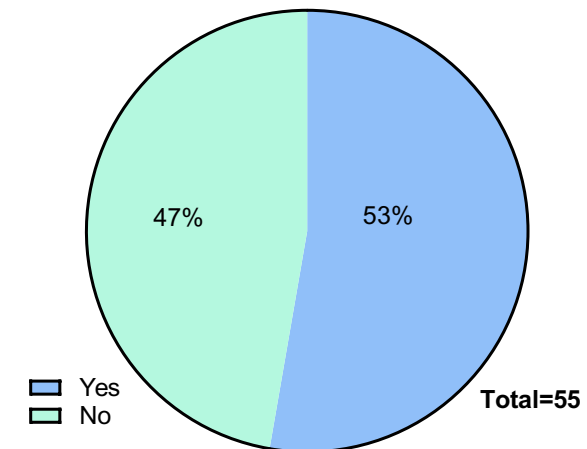
Multidisciplinary care

- Agreement on need for multidisciplinary collaboration, but great variability of formal structures across centres
- Often cooperation of metabolic specialists with local obstetric services
- Written protocols and interdisciplinary consultation support safe maternal and fetal care

Metabolic dietician to guide dietary management during pregnancy

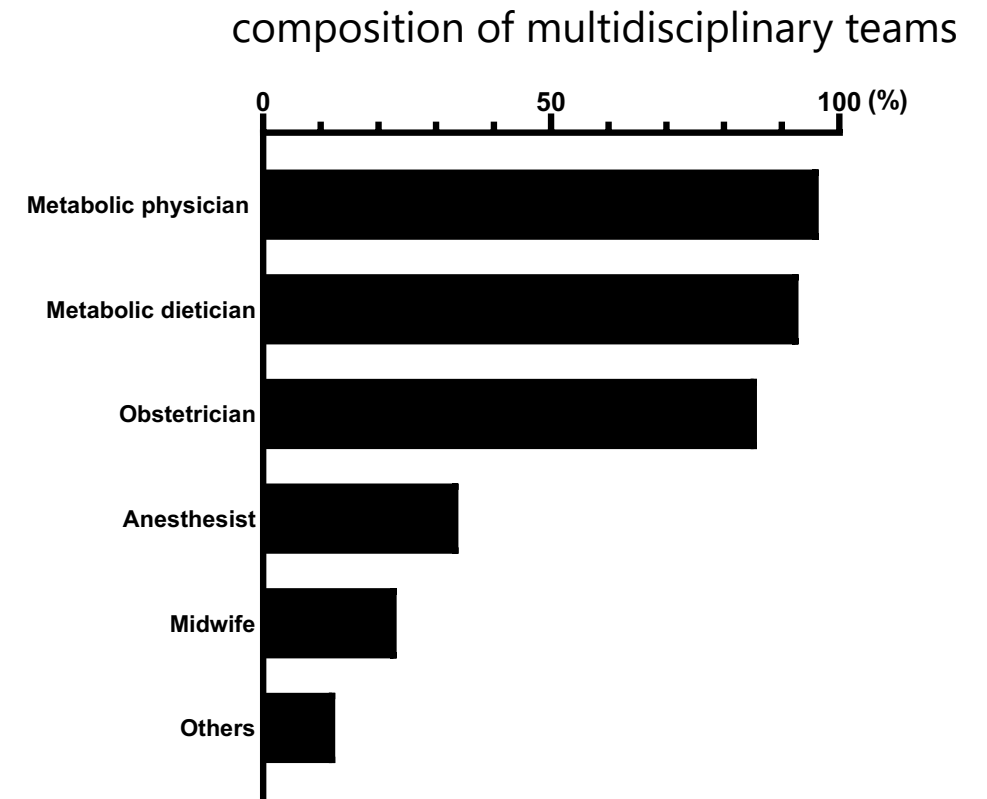


Obstetrician with experience in managing pregnancies in patients with inborn errors of metabolism



Multidisciplinary care

- Regular multidisciplinary meetings during pregnancy (metabolic/obstetric) in only 58% of centres
- Outpatient consultations involving both obstetric and metabolic specialists were arranged in an interdisciplinary fashion in 53% of centres
- Anesthetists or midwives were often involved on indication, rather than routinely



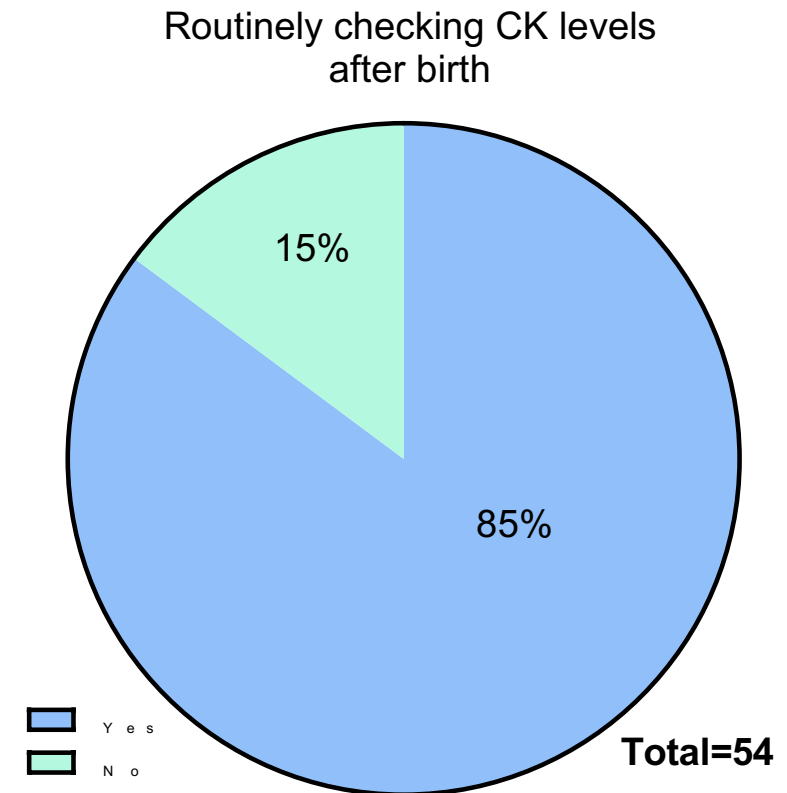
Delivery setting



- Delivery in centres with metabolic expertise strongly encouraged (93%)
- Delivery location decisions often depend on practical considerations such as patient metabolic stability, geographic proximity, and local healthcare resources.
- Women with milder phenotypes or stable disease might safely deliver closer to home or in non-specialized centers, while those with severe or unstable metabolic conditions ideally deliver at specialized centers with intensive care availability

Postpartum creatine kinase monitoring

- Duration and frequency of recommended monitoring highly variable
- Tailored to the patient's metabolic stability, disease severity, symptoms, and dietary intake



Conclusions

- Broad agreement on the importance of preconception counseling and dietary adaptation during pregnancy and the use of CK as a monitoring parameter during pregnancy and peri- and postpartum
- Substantial variability persists in monitoring intensity, postpartum surveillance, and neonatal follow-up, indicating areas where clinical practice remains largely experience-based
- Multidisciplinary care is widely endorsed in principle but inconsistently formalized in practice

Need for structured consensus processes/guidelines

THANK YOU