Associazione Svizzera Farmacologia Perinatale
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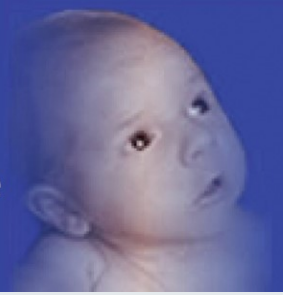
Swiss Association Perinatal Pharmacology



SGGG 28.6.19 Workshop Nr. 15 / SAPP

Interaktionen von wichtigen Medikamenten in Schwangerschaft und Stillzeit

Interactions of daily used drugs in pregnancy and lactation

Interactions des médicaments principaux en grossesse et en allaitement

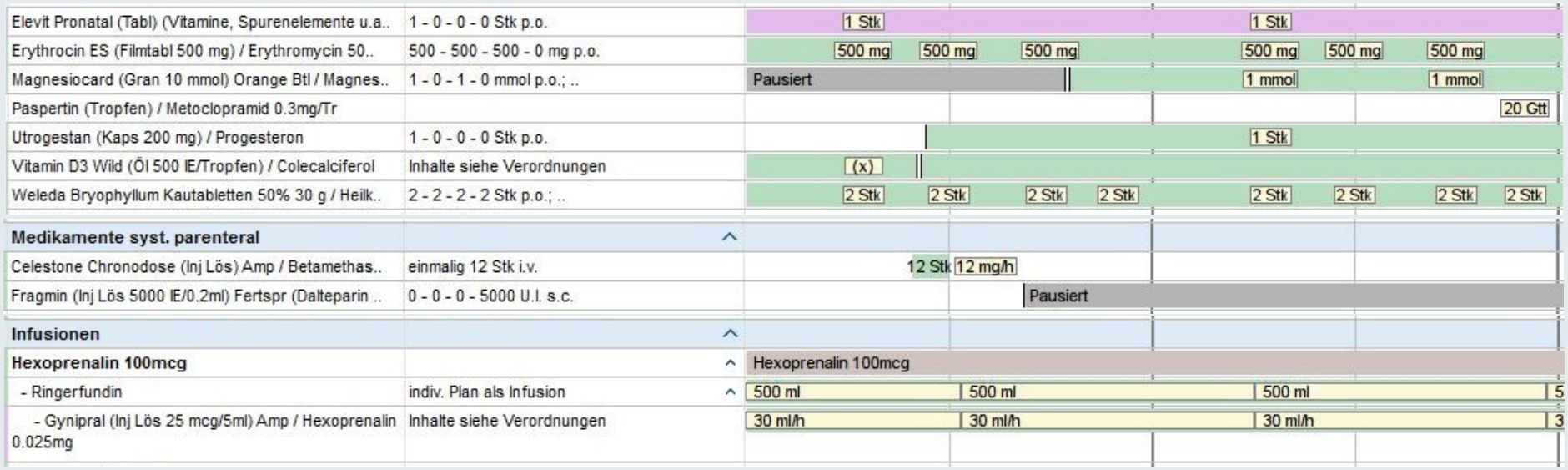
Andrea Burch, Zürich

Olav Lapaire, Basel

USZ Universitäts Spital Zürich

Universitätsspital Basel

Primipara, maternal age 38, 26+2 gestational weeks, PPROM, risk at preterm labour



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Primipara, maternal age 38, 26+2 gestational weeks, PPROM, risk at preterm labour

- Syncope on the toilet after *nausea* and *vomiting*
- Transfer to the delivery room, start with magnesium sulfate
- Neurological examination: no hint for an epileptic or preeclamptic event

→ Reasons for clinical symptoms?

Drug-drug interaction (DDI)

Change in efficacy or toxicity of one drug by prior or concomitant administration of a second drug

→ Pharmacodynamic interactions

→ Pharmacokinetic interactions

No data available about “incidence” of DDI during pregnancy and breastfeeding

Parameter	Consequences
Delayed gastric emptying and increased gastric pH	Altered drug bioavailability
Increased cardiac output	Increased hepatic blood flow-increased elimination
Increased total body water, extracellular fluid	Altered drug distribution
Increased fat stores	Increased distribution and decreased elimination of lipid soluble drugs
Increased renal blood flow and glomerular filtration rate	Increased renal clearance
Decreased maternal albumin	Altered free fraction
Altered CYP450 activity and UGT activity (Human UDP-glucuronosyltransferase)	Altered systemic absorption and hepatic metabolism

Koren G et al. 2018

Drug-drug interaction (DDI)

A broad spectrum of physiological changes during pregnancy, e.g.:

- Liver function - responsiveness of cytochrome P450 enzymes (polymorphism) influence on drug effect:

  CYP2D6 increased

  CYP3A4 increased

  CYP1A2 decreased

- Liver, kidney function: Drug transporters (polymorphism)

Faqi and Holm 2016

Drug-drug interaction (DDI)

A broad spectrum of physiological ch… …nancy.
e.g.:

- Liver function - respons… …ome P450 enzymes (polymo…
  - CYP2D…
  - CY…
  - CYP… …eased
- Liver, kidney function: Drug transporters (polymorphism)

Prediction of pharmacokinetics and pharmacodynamics: How? Clinical investigations are needed!

Faqi and Holm 2016

Drug-drug interaction (DDI)

- Significant gap between accumulating knowledge of pharmacokinetic changes in pregnant and lactating women and our understanding of their clinical impact for mother and fetus or baby, respectively.

→ Implicates also the lack of knowledge of the clinical influence on drug-drug interactions

Pariente G et al. 2016

Interactions of drugs used in Obstetrics

Betamimetics	↔ Glucocorticosteroids (LRI) ↔ Betablockers
Antidiabetics (insulin, metformin)	↔ Glucocorticosteroids
Folic acid metabolism	↔ Cotrimoxazole
Iron	↔ Magnesium salts ↔ Antacids

Interactions of drugs used in Obstetrics

Contin.

Betamethasone, nifedipine, progesterone	↔ Inhibitors/inductors of CYP3A4 (ein Isoenzym aus dem Cytochrom P450-System)
Ursodeoxycolic acid	↔ Progesterone (e.g. Utrogestan)

Betamimetics (I)

↔ Glucocorticoids (LRI):

- Pulmonary edema is a complication of a $ß_2$-sympathomimetic treatment
- Betamethasone and dexamethasone have minimal mineralocorticoid activity, nevertheless, fluid retention due to corticosteroid administration is possible

→ Additional risk for pulmonary edema

Fluid restriction during therapy

LRI: lung ripening induction

Betamimetics (II)

Different strategies

USB

Conservative fluid restriction during therapy

USZ

Combination with glucocorticoids (LRI):

In case of missing infection and amnion infection syndrome:

- Monitoring fluid balance (12-hours) AND
- Fluid intake restriction (1000 ml)

ABSTRACT

A case of severe pulmonary oedema during beta$_2$-adrenergic agonist tocolytic therapy (salbutamol) in a pregnant woman admitted for preterm labor at 32 weeks of amenorrhoea is reported. Echocardiography and haemodynamic investigations did not show any left ventricular systolic or diastolic dysfunction.

Samet A et al. 2000

British Journal of Obstetrics and Gynaecology
April 2000, Vol 107, pp. 439–444

REVIEW

The pathophysiology of pulmonary oedema with the use of beta-agonists

Introduction

Preterm delivery is the major cause of perinatal mortality and morbidity in the developed world[1]. This has led to attempts to inhibit preterm labour by the use of tocolytic agents. Despite this, over the last two to three decades, the incidence of preterm birth has not decreased. A number of tocolytic agents are currently used in an effort to prevent preterm birth, such as beta-agonists, prostaglandin synthetase inhibitors and calcium channel blockers, but while these agents have been shown to stop contractions, they have not been shown to be associated with a reduction in perinatal mortality or morbidity[2,3]. In addition, the tocolytics currently used have potentially serious fetomaternal side effects[4].

hydrostatic and colloid osmotic pressures according to the equation of Starling[10]:

$$F = CFC\ [\ (P_c\text{-}P_i) - \sigma\ (COP_p\text{-}COP_i)],$$

where F is the net capillary filtration, CFC the capillary filtration coefficient and σ is the reflection coefficient; P_c and P_i are the hydrostatic pressures in the capillary and interstitium, respectively; COP_p and COP_i are the colloid osmotic pressures of plasma and interstitial fluid, respectively.

Pregnancy is accompanied by physiological adaptations which bring about changes in the value of several components of the Starling equation. By measuring these changes, it may be possible to find out why pregnant women are more prone to develop oedema. The

Lamont RF 2000

Pulmonary edema and Beta-agonists

Maternal factors

Fluid balance

Fetal factors

Multiple pregnancy

Tocolytic associated factors

Positive fluid balance

Cardiovascular effects

Beta-agonists produce a general vasodilatation which leads to systolic hypotension

Concomitant use of glucocorticoids

Infection

Betamimetics (II)

Different strategies

USB

Conservative Fluid restriction during therapy

USZ

Which one is adequat?

Combination with glucocorticoids (LRI):

In case of missing infection and amnion infection syndrome:

- Monitoring fluid balance (12-hours) AND
- Fluid intake restriction (1000 ml)

Betamimetics (III)

↔ Betablockers

- Possible attenuation of the tocolytic effect of betamimetics (hexoprenalin)
- Competitive antagonism of $ß_2$-receptors (bronchial system and uterus)

→ Dependent on beta receptor blocking's selectivity:

selective (e.g.): bisoprolol, metoprolol, atenolol

unselective (e.g.): carvedilol, labetalol, propranolol

Betamimetics (IV)

↔ Betablockers

If treatment with beta blocking agents is essential:

use of cardioselective betablocker

→ Higher doses of betamimetics are possibly required

Antidiabetics (insulin, metformin)

↔ Glucocorticoids (LRI):

- Blood glucose↑ by decreasing tissue insulin sensitivity, stimulating gluconeogenesis and reducing peripheral glucose utilization

Careful monitoring and adjusted therapy

LRI: lung ripening induction

Kurve | Anordnungen | Ärzte | Pflege | Therapeuten | Befunde/Formulare | Stammdaten — FK Schwangeren… — Stäger, Elisabeth

Kurve | Schwangerschaft/Geburt | Überwachungsbögen | Blutzuckerkurve | Austrittsplanung

Körpermaße	84.4 kg, 160 cm, BMI: 33 kg/m², BSA: 1.94 m²	**Diabetes-Typ**	Unbekannt	**Bemerkungen / Besonderheiten**	Diabetesberatung: Franziska Gasche 86110 misst und spritzt selber
Diagnosen	43-jährige Patientin G V P III in der 26+3 SSW (ET 06.09.2019) mit Dichorialer Diamnioter Geminigravidität und vorzeitigen portiowirksamen Kontraktionen mit	**Therapie**	keine		
Delir		**Risiko Mangelern.**		**Sturz-Risiko**	**Dekubitus-Risiko**

15.05. 16.05. 17.05. 18.05. 19.05. 20.05. 21.05. 22.05. 23.05. 24.05. 25.05. 26.05. 27.05. 28.05. 29.05. 30.05. 31.05. 01.06. 02.06. 03.06. 04.06. 05.06. 06.06. 07.06. 08.06. 09.06. 10.06. 11.06. 12.06. 13.06. 14.06. 15.06. 16.06. 17.06. 18.06. 19.06. 20.06. 21.06. 22.06. 23.06. 24.

	So 02.06.2019	Mo 03.06.2019	Di 04.06.2019	Mi 05.06.2019	Do 06.06.2019
Diabetes-Kurve					
BZ 26.0 / 23.1 / 20.2 / 17.3 / 14.4 / 11.6 / 8.7 / 5.8 / 2.9 / 0.0	08:00 16:00	08:00 16:00	08:00 16:00	08:00 16:00	08:00 16:00
Mahlzeiten					
Frühstück					
Mittagessen					
Abendessen					
Langwirksame Insuline					
Insulin Levemir 100 U/ml Injektionslösung				8 U √	8 U √
Diabetestherapie					
Insulin Levemir 100 U/ml Injektionslösung				8 U √	8 U √
Stationslabor					

2x Celestone chronodose
3./4.Juni 2019

6.4 11.1 7.8 10.9 12.1 11.9 11.4 15.2 8.4 10.2 11.5 12.8 11.7 7 12.8 8.1 8.7 7.9 10.2

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Folic acid metabolism

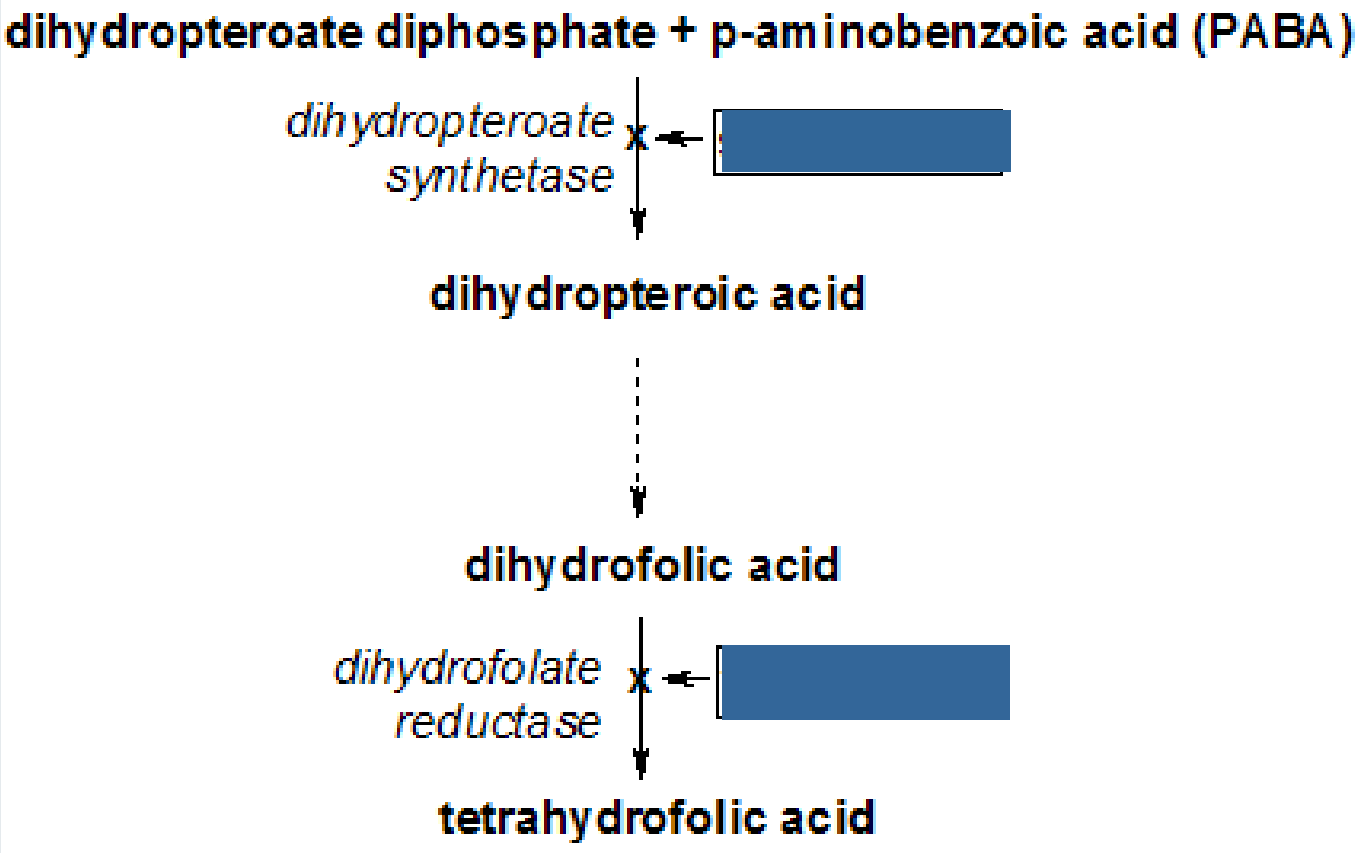
↔ Cotrimoxazole

- Evidence of relation btw. folic acid deficiency and neural tube defect
- periconceptional folic acid supplementation could decrease the occurrence or recurrence of Neural Tube Defects (NTDs) by 40% to 70%.

Imbard et al. 2013

MRC Vitamin Study Research Group. Lancet.1991;338:131-13

Cotrimoxazol



©Wikipedia

Folic acid metabolism

↔ Cotrimoxazole

- Evidence of relation btw. folic acid deficiency and neural tube defect

→ Increased teratogenic risk of folic acid antagonists

Supplementation of folic acid (high-dose: 5 mg) during therapy

Imbard et al. 2013

Iron

↔ Magnesium salts

- Polyvalent cations build hardly soluble, poorly absorbable complexes

↔ Antacids

- Fe(II)-salts are badly absorbed due to higher pH of the stomach (oxidation to Fe(III) already in stomach)

Fe(II)-salts should be taken 2 hours before polyvalent cations or antacids

Obstetric drugs metabolized by CYP3A4

- **Inhibition** of enzyme activity of CYP3A4 by a concomitant drug: **erythromycin, grapefruit juice**
- **Induction** of enzyme activity of CYP3A4 by a concomitant drug: **St. John's worth**
- **Metabolized** by CYP3A4:

  Nifedipine

  Progesterone

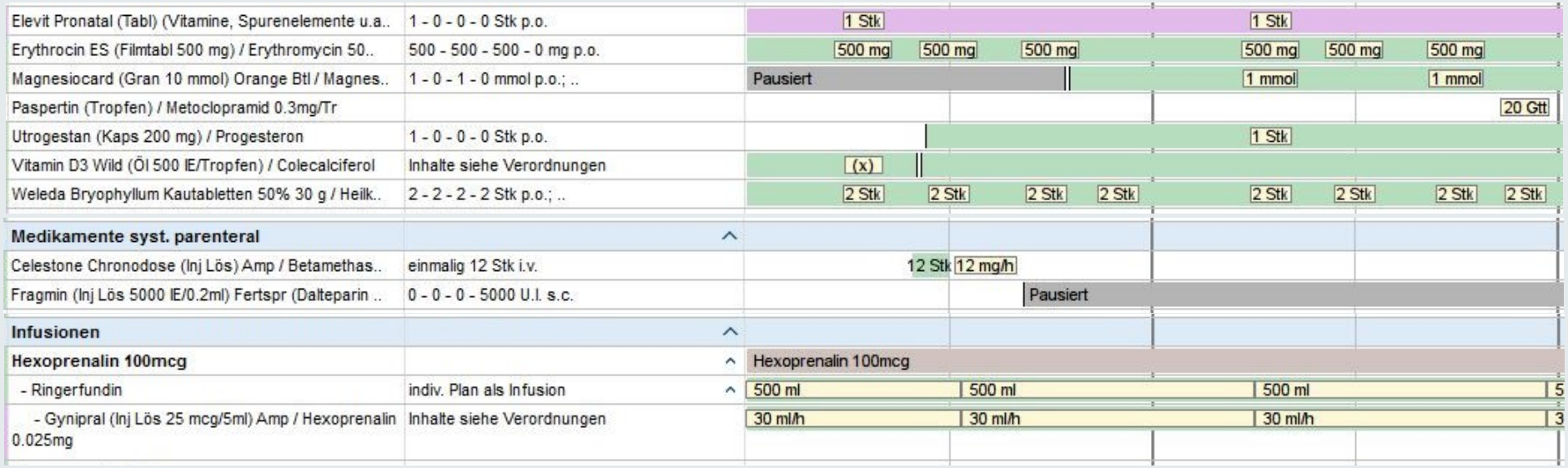
  Betamethasone

Obstetric drugs metabolized by CYP3A4

Possible effects modulating:

- **Bioavailability**
- **Accumulation/elimination of a drug**
- **Accumulation of toxic metabolites**

Primipara, maternal age 38, 26+2 gestational weeks, PPROM, risk at preterm labour



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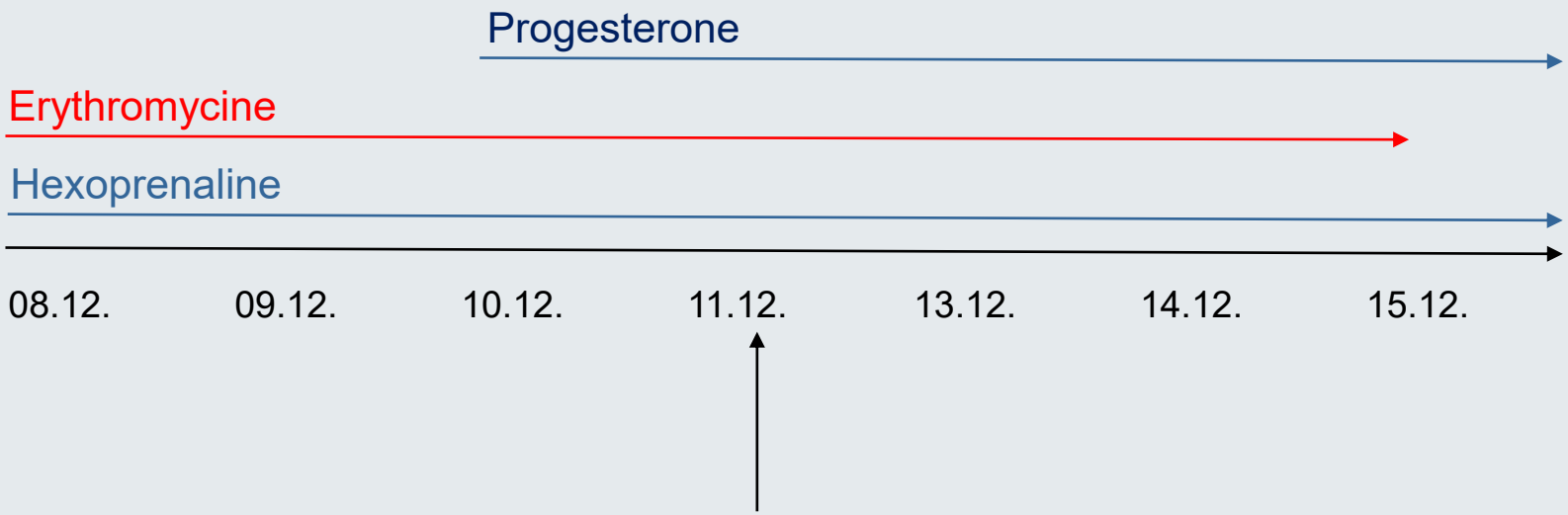
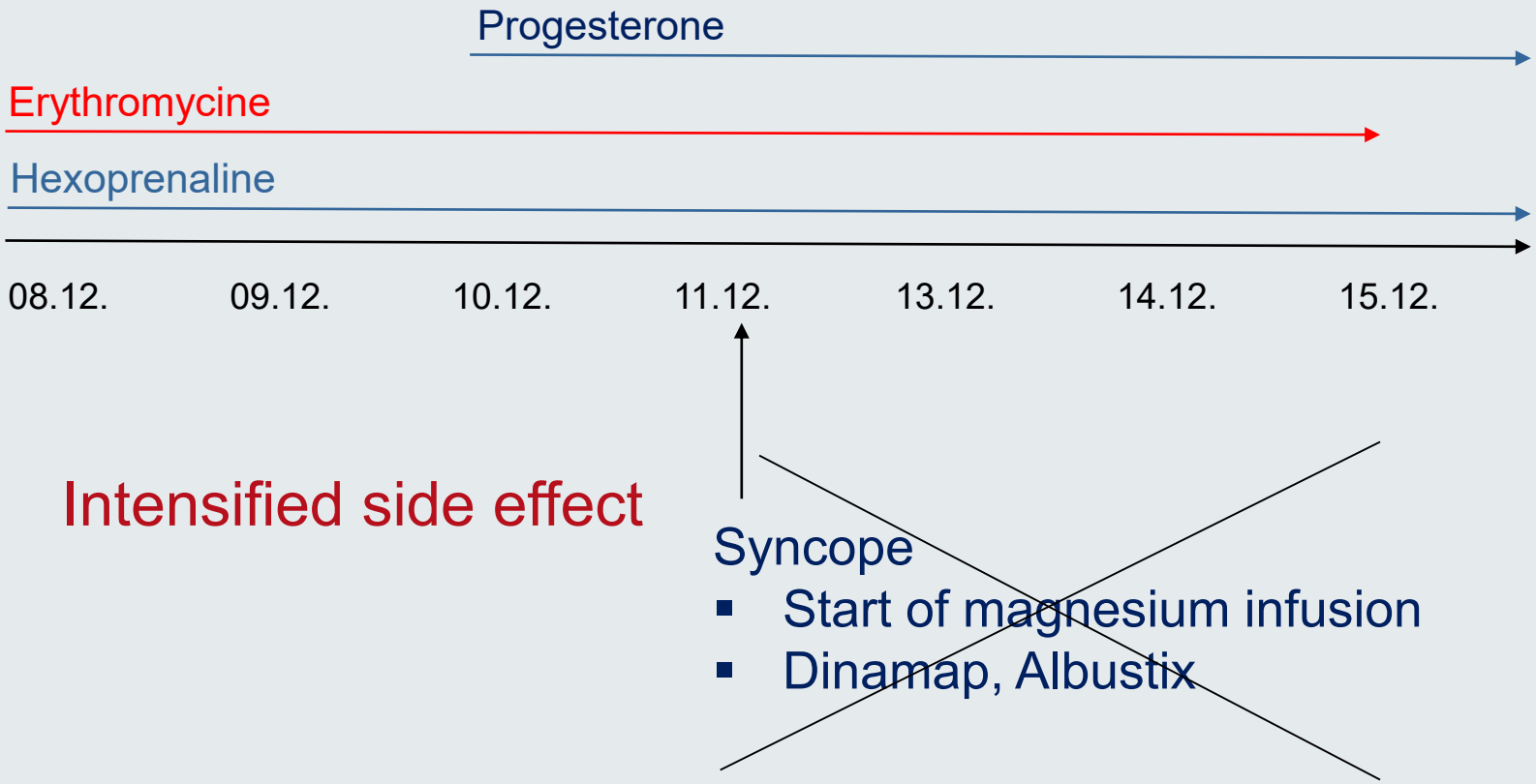
Primipara, age 38, 26+2 gestational weeks, PPROM, preterm labour



Syncope

- Start of magnesium infusion
- Dinamap, Albustix

Primipara, maternal age 38, 26+2 gestational weeks, PPROM, risk at preterm labour



Ursodeoxycholic acid ↔ Progesterone

PLoS One. 2016 Aug 5;11(8):e0159203. doi: 10.1371/journal.pone.0159203. eCollection 2016.

A Comprehensive Evaluation of Steroid Metabolism in Women with Intrahepatic Cholestasis of Pregnancy.

Pařízek A[1], Hill M[2], Dušková M[2], Vítek L[3], Velíková M[2], Kancheva R[2], Šimják P[1], Koucký M[1], Kokrdová Z[1], Adamcová K[1], Černý A[1], Hájek Z[1], Stárka L[2].

Author information

Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a common liver disorder, mostly occurring in the third trimester. ICP is defined as an elevation of serum bile acids, typically accompanied by pruritus and elevated activities of liver aminotransferases. ICP is caused by impaired biliary lipid secretion, in which endogenous steroids may play a key role. Although ICP is benign for the pregnant woman, it may be harmful for the fetus. We evaluated the differences between maternal circulating steroids measured by RIA (17-hydroxypregnenolone and its sulfate, 17-hydroxyprogesterone, and cortisol) and GC-MS (additional steroids), hepatic aminotransferases and bilirubin in women with ICP (n = 15, total bile acids (TBA) >8 μM) and corresponding controls (n = 17). An age-adjusted linear model, receiver-operating characteristics (ROC), and multivariate regression (a method of orthogonal projections to latent structure, OPLS) were used for data evaluation. While aminotransferases, conjugates of pregnanediols, 17-hydroxypregnenolone and 5β-androstane-3α,17β-diol were higher in ICP patients, 20α-dihydropregnenolone, 16α-hydroxy-steroids, sulfated 17-oxo-C19-steroids, and 5β-reduced steroids were lower. The OPLS model including steroids measured by GC-MS and RIA showed 93.3% sensitivity and 100% specificity, while the model including steroids measured by GC-MS in a single sample aliquot showed 93.3% sensitivity and 94.1% specificity. A composite index including ratios of sulfated 3α/β-hydroxy-5α/β-androstane-17-ones to conjugated 5α/β-pregnane-3α/β, 20α-diols discriminated with 93.3% specificity and 81.3% sensitivity (ROC analysis). These new data demonstrating altered steroidogenesis in ICP patients offer more detailed pathophysiological insights into the role of steroids in the development of ICP.

PMID: 27494119 PMCID: PMC4975406 DOI: 10.1371/journal.pone.0159203

Parizek A et al. 2016

HEPATOLOGY, VOL. 63, NO. 4, 2016

Sulfated Progesterone Metabolites in the Pathogenesis of Intrahepatic Cholestasis of Pregnancy: Another Loop in the Ascending Spiral of Medical Knowledge

Reyes H 2016

- Participation in the pathogenesis of intrahepatic cholestasis of pregnancy (ICP)
- Involvement in the pathogenesis of maternal pruritus
- Prediction of the onset ICP

Summary

Drug	Influenced by drug	Clinical impact
betamimetics (group)	glucocorticoids (group)	additive risk of lung edema
betamimetics (group)	betablockers (group)	pharmacodynamic effect neutralized, lack of efficacy
antidiabetics (insulin, metformin)	glucocorticoids (group)	lack of efficacy of the antidiabetic due to gluconeogenesis
folic acid metabolism	cotrimoxazole	undersupply of folic acid
iron	magnesium salts/ antacids	reduction of absorption

Summary

Drug	Influenced by drug/food	Clinical impact
nifedipine	grapefruit juice	excessive exposure, adverse effects ↑
nifedipine	erythromycin	excessive exposure, adverse effects ↑
progesterone	erythromycin	‘’
betamethasone	erythromycin	‘’
several	St. John’s worth	lack/reduction of efficacy
progesterone	ursodeoxycholic acid	induction of a cholestatic icterus by progesterone

Take home message

- A broad spectrum of physiological changes during pregnancy and lactation and possible polymorphisms make drug-drug interactions (DDI) more likely
- Lack of knowledge about incidence of DDI during pregnancy and lactation
- Different sights about clinical impact on DDI

But: understanding of physiology as well as pharmacological mechanisms helps preventing / monitoring DDI.

→ Research!!!

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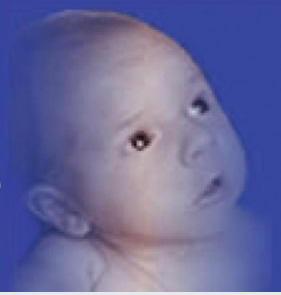

Evidence-based data on drugs and therapies in pregnancy and lactation:

Swiss Association of Perinatal Pharmacology, SAPP

Schweizerische Arbeitsgemeinschaft für Perinatale Pharmakologie, SAPP

Visit our homepage: www.sappinfo.ch

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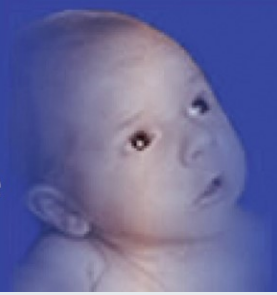

Schweizerische Arbeitsgemeinschaft Perinatale Pharmakologie

Swiss Association Perinatal Pharmacology

NEW !

SAPP Data on AmiKo (D) and CoMed (F) (Drug compendium)

Drugs indications and dosages in pregnancy and lactation

www.sappinfo.ch

(D)

(F)

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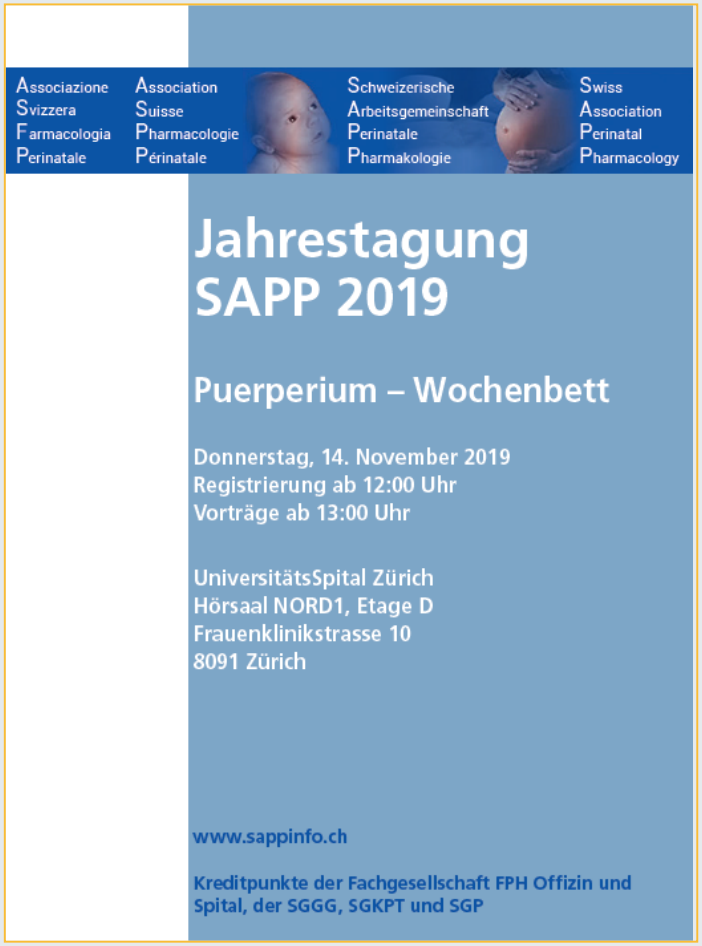
Annual meeting 2019

14.11.2019, Univ.spital Zürich



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Lunch Symposium SGGG 2020

Bryophyllum pinnatum

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Universitätsspital Basel

Andrea Burch, Zürich

Olav Lapaire, Basel

See you on our next SAPP meeting!

Interaction databases

Pharmavista®, HCI Solutions AG 2019
IBM Micromedex®, Truven Health Analytics 2019
Product informations (2019)

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