INSELSPITAL
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RHEUMATOLOGIE
& IMMUNOLOGIE

EULAR Highlights 2021

Schwangerschaft bei Rheumaerkrankungen

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Safety of **TNF inhibitors** during pregnancy

Prospective study in **Systemic Sclerosis**

Retrospective analyses in **APS**, **TA**

Analysing cord blood levels of TNF inhibitors to validate the EULAR points to consider for TNF inhibitor use during pregnancy

Ghalandari N, Kemper E, Crijns HJMJ, Smeele HTW, Dolhain RJEM; Erasmus MC, Rotterdam

Background

- Drawback of prescribing TNFi during pregnancy is placental transfer via FcRn
- EULAR points to consider for the use of TNFi during pregnancy
  - **Stop** at gestational **week 20**: **infliximab, adalimumab**
  - **Stop** at gestational week **30-32**: **etanercept**
  - **Consider for use throughout** pregnancy: **certolizumab**

Objective

to validate EULAR points to consider by analysing TNFi in cord blood

Results

Cord blood measurement in n=137

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	Certolizumab (n=68)	Etanercept (n=30)	Adalimumab (n=25)	Infliximab (n=14)
Gestational age at time of stopping TNFi, median, IQR (weeks)	37.0 (34.1-38.1)	25.0 (17.9 -28.0)	19.0 (12.4-19.9)	18.4 (14.0 – 20.1)
Maternal concentration of TNFi in **1rt trimester**, median, IQR (µg/ml)	24.6 (19.0 – 31.0)	2.1 (0.8 – 2.25)	8.2 (1.5 – 10.0)	14 (8.0 – 21.0)
Maternal concentration of TNFi in **3rd trimester**, median, IQR (µg/ml)	20.5 (13.0-29.6)	0.2 (0.2 – 0.7)	0.9 (0.1 – 1.4)	1.4 (0.1 – 1.9)
Concentration of TNFi in the **cord blood**, median, IQR, (µg/ml)	0.3 (0.2 – 1.3)	-	0.5 (0.2 – 0.7)	0.4 (0.1 – 1.2)

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Conclusions

Compliance with EULAR points to consider[1] results in

- CZP, Etanercept:

  undetectable or absent levels in most patients

- IFX, ADA:

  detectable in neonatal cord blood of about 50% of patients,

  levels far lower than maternal levels

[1] EULAR points to consider 2016 (Götestam Skorpen C et al, Ann Rheum Dis 2016

Pharmacovigilance Pregnancy Data in a Large Population of Patients with Chronic inflammatory diseases exposed to Certolizumab Pegol: Pregnancy Outcomes and Confounders

Clowse M, Fischer-Betz R, Nelson-Piercy C, Scheuerle AE, Kumke T, Lauwerys B, Kasliwal R, Förger F

Background:

Certolizumab pegol (CZP), a PEGylated, Fc-free TNFi with no/minimal placental transfer

Objective:

To assess pregnancy outcomes from UCB Pharmacovigilance safety database from prospectively reported pregnancies exposed to CZP

Methods:

UCB Pharmacovigilance safety database, up to Nov 2020

Evaluation of confounders by stepwise regression model:

- specific chronic inflammatory diseases
- non-biologic medications
- maternal infections

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Result:

1392 prospective pregnancies:

RA (643), axSpA (215), PsA (113), Crohn's disease (293), PsO (61), others (112)

CZP exposure: 73.3% in 1st trimester, 39.5% in all trimesters

Normal rates for

live births (88.4%)

abortions (10.5%)

preterm delivery (9.8%)

congenital malformations (2.5%), no pattern

Confounders

preterm associated with; corticosteroids, maternal infection

low birth weight associated with: corticosteroids, RA

pregnancy loss associated with: NSAIDs, MTX/Lef, Crohn's disease

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Conclusions

No adverse pregnancy outcome safety signals

No congenital malformation signals, no pattern

International Multicenter Prospective Study on PREgnancy in Systemic Sclerosis (IMPRESS-2)

Tombetti E, Ramoni V, Betelli M, Allanore Y, Atzeni F, Baresic M, Veneventi F, Bosello S, …., Brucato A

Background

Generally favourable obstetric outcome in SSc

Higher-than normal risk of adverse pregnancy outcomes

Little prospective data

IMPRESS-2 study:

Prospective controlled study, time: 9 months pregnancy + 12 months postpartum

- SSc pregnancies and inherent offspring (n=110)
- Control pregnancies and inherent offspring (n=218)
- SSc non-pregnant (n=78, 21 months follow-up)

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Baseline characteristics

Age	32
Disease duration (mts)	78
Diffuse, limited	33%, 55%
ACA, ATA, aRNA po	29%, 45%, 6%
mRSS	5.7
FVC (% predicted)	95
DLCO (% predicted)	78

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Results

Mother death	0
Miscarriages	7 (6%)
Foetal death	4 (4%)
Voluntary abortions	1(1%)
Infant mortality	2(2%)

Any maternal/ foetal complication: 47 (43%)

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Result: Obstetric outcome

	SSc pregnancies	Control pregnancies	P-value
Gestational Hypertension	12 (11%)	8 (4%)	0.004
Preeclampsia	9 (8%)	3 (1%)	0.002
Eclampsia	1 (1%)	0(0%)	ns
Foetal growth restriction	13 (12%)	9 (4%)	0.004
PROM	10 (9%)	11 (5%)	0.099
Caesarean section	52 (47%)	8 (4%)	0.002
Pregnancy duration			
Preterm delivery <37 w	26 (24%)	16 (7%)	<0.001
Preterm delivery <34 w	14 (13%)	5 (2%)	<0.001

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Result: Paediatric outcomes

	SSc mothers	Control mothers	P-value
Weight at birth, g	2773	3243	<0.001
Very low birth weight	7 (7%)	2 (1%)	0.005
Small for gestational age	18 (18%)	36 (12%)	0.005
Neonatal malformations	5 (5%)	4 (2%)	n.s.
Admission of neonatal ICU	11 (12%)	2 (1%)	<0.001
Infant mortality	2 (2%)	0	n.s.
Complications 1st year	2 (2%) bronchiolitis	0	n.s.
Weight at 1 year (kg)	9.9	9.8	n.s.
Height at 1 year (cm)	75	75	n.s.

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Result: Risk factor for adverse pregnancy outcome

- Preeclampsia, gestational hypertension
  - Protective: CCB (estimate -2.2)
  - Risk factors: arterial hypertension (estimate 18,0), baseline immunosuppression (estimate 3.5), Iloprost (estimate 3.5)
- Low birth weight
  - Protective: CCB (estimate -3.8)
  - Risk factors: anti-ScL70 (estimate 4.4), Steroid use during preg (estimate 6.1), PPI (3.9) , Iloprost (9.0)

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Conclusions

Pregnancy Outcome

Outcome of pregnancy generally favourable

Increased risk of gestational hypertension, preeclampsia, prematurity, ↓fetal growth

No long-term effect in children at 1 year

Risk factors: baseline immunosuprressive agents, iloprost, PPIs

?placental insufficiency

Disease

No effect of pregnancy on SSc course

LOW PRECONCEPTIONAL COMPLEMENT LEVEL IS RELATED WITH ADVERSE OBSTETRIC OUTCOME IN A MULTICENTRIC COHORT OF PREGNANCY IN PATIENTS WITH APS AND aPL POSITIVITY

Lini D, Nalli C, Andreoli L, …. Tincani A

Aim:

to analyse the association of preconceptional decrease of complement in APS /aPL carriers with adverse pregnancy outcome.

Methods:

Multicenter study (Italy, Russia): **260 pregnancies**

Adverser pregnancy outcome:

- preterm < 37 week gestation
- pregnancy loss (abortion <10 w, fetal loss >10w)
- Preeclampsia, eclampsia, HELLP

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Lini D, Nalli C, Andreoli L, …. Tincani A

Results:

- **low complement** (C3 and/ or C4) at preconception in 93 (**36%**) of all pregnancies
  - 71 APS
  - 22 aPL carriers
- **Adverse pregnancy outcome** [94 APS (51%); 21 aPL carriers (29%)]

  more often seen in APS, aPL with low C3 and low C4 at preconception

low C3/C4 in APS, aPL -> preterm delivery

-> pregnancy losses (abortion, fetal death, neonatal death)

especially in triple aPL positivity

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Lini D, Nalli C, Andreoli L, …. Tincani A

Conclusion:

- Check complement levels in patients with APS /aPL planning a pregnancy

FERTILITY AND PREGNANCY OUTCOMES IN TAKAYASU'S ARTERITIS

Taghiyeva A, Kilic L, Cagan M, Bolek EC, Yardimci GK, Karadag O, Ozyuncu O, Bilgen SA

Aim:

- To evaluate fertility and pregnancy outcomes in TAK before and after diagnos

Methods:

- Database of Hacettepe University Vasculitis Research Center (HUVAC, Turkey)
- 120 female TA
  - No history of pregnancy in **38** patients
  - 233 pregnancies in **82** TA patients
    - 100 before TA diagnosis
    - 33 after TA diagnosis (C1: 15.7%, C2: 47.3%, C3: 31.5%)

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Results:

- Infertility in TA : 12.5% ↑ [general population :8.1%]
- Early menopause (<45y) in TA: 16.7% ↑ [general population :7.6%]

- Pregnancy outcomes in TA
  - Maternal complication:
    Gestational hypertension (more frequent in preg after TA diagnosis)
  - Fetal complications:
    prematurity, low birth weight /IUGR (more frequent in preg after TA diagnosis, ns)

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Taghiyeva A, Kilic L, Cagan M, Bolek EC, Yardimci GK, Karadag O, Ozyuncu O, Bilgen SA

Conclusions

- Data suggest increased infertility rate in TA
- Pregnancy in TA is associated with maternal (RR↑) and fetal risks