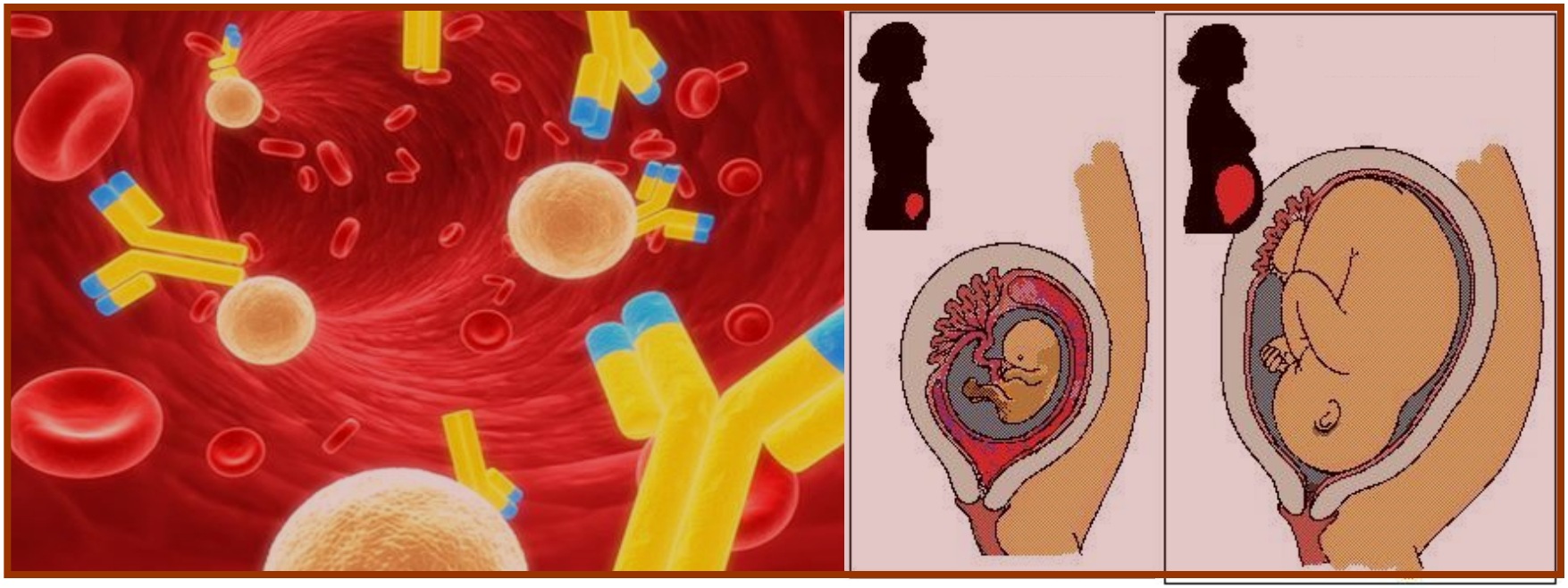
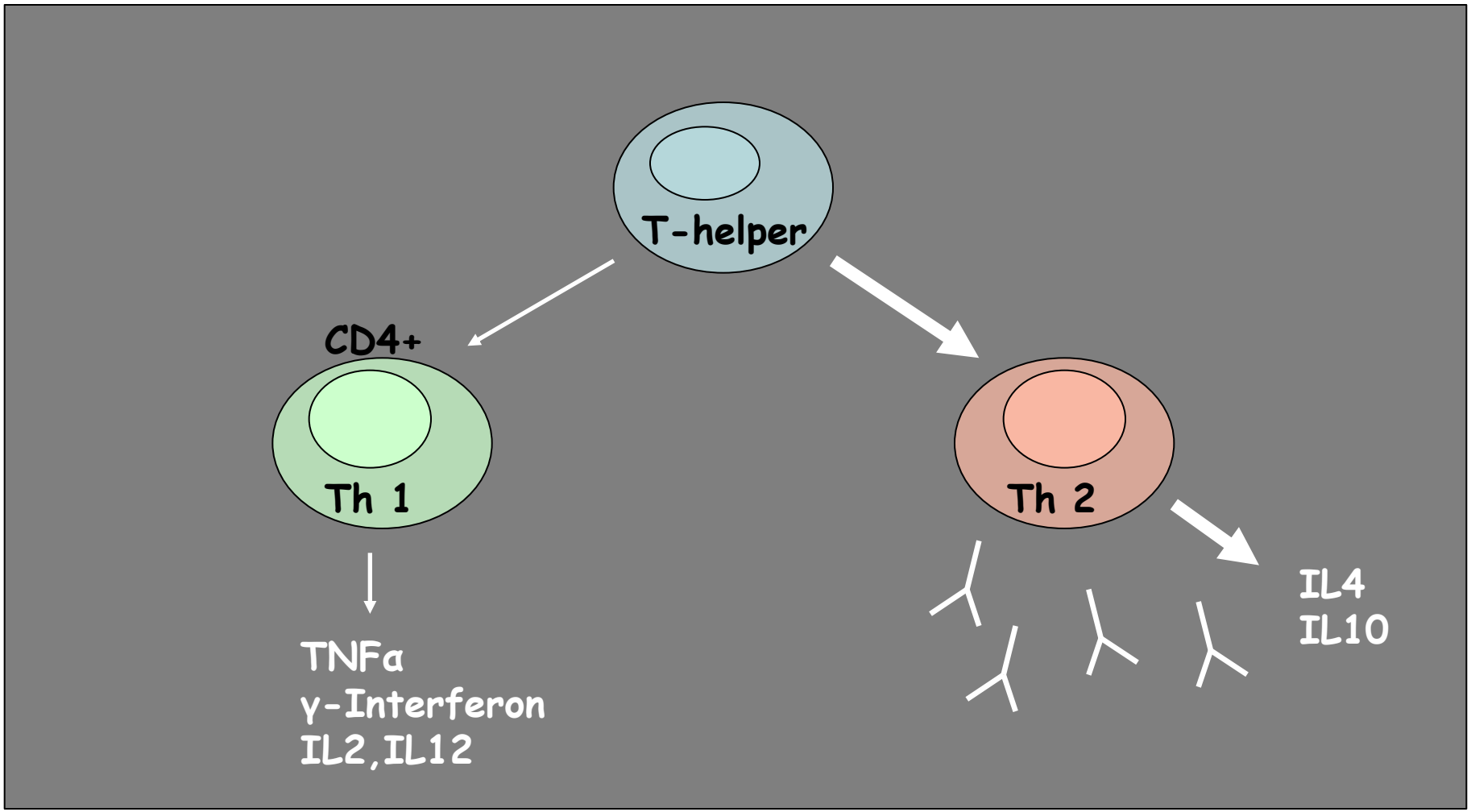
PREGNANCY AND AUTOIMMUNE DISORDERS



Maternal - Fetal Tıp ve Perinatoloji Derneği Türkiye 23-06-1998

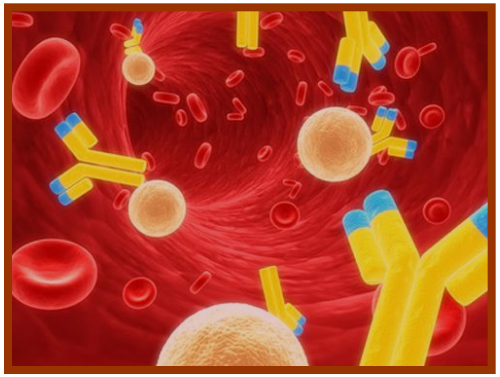
Prof. FİLİZ F. BİLGİN YANIK, MD.

IMMUNE SYSTEM IN PREGNANCY



AUTOIMMUNE DİSORDERS

- Abnormal immune response against ones own cells or tissues
- More common in women
- More common during the reproductive period



PREGNANCY AND AUTOIMMUNE DISORDERS

- The autoimmune disorder may have adverse effects on pregnancy.
- Pregnancy may affect the course of the autoimmune disorder.
- Transplacental passage of auto-antibodies may affect the fetus and newborn.
- In the postpartum period, the hormonal changes and/or fetal cells remaining in the maternal circulation (microchimerism) may induce the development of autoimmune disorders or may affect the course of the pre-existing disorders.

PREGNANCY AND AUTOIMMUNE DISORDERS

- Thyroid diseases
- SLE
- Rheumatoid arthritis
- Ankylosing spondylitis
- Antiphospholipid syndrome (APS)

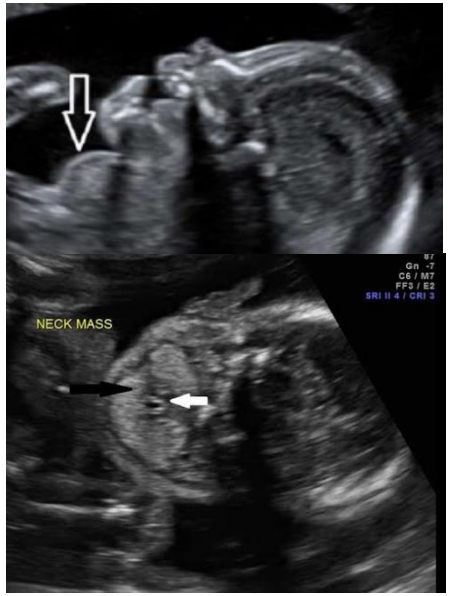
PREGNANCY AND AUTOIMMUNE THYROID DISEASES I

- Hyperthyroidism in pregnancy: 1-4/1000
- Most common causes: hCG induced hyperthyroidism or Graves' disease
- Subclinical hyperthyroidism (low TSH, normal fT4 levels) may be considered to be physiological.
- Graves' disease: TSH- receptor stimulating antibodies (**TRAb** – TSI and TBII)
- TSH levels are very low (<0,01 mU/L) and fT4 levels are high.

PREGNANCY AND AUTOIMMUNE THYROID DISEASES II

Adverse Pregnancy Outcomes in Graves' Disease:

- Abortion
- PTD
- SGA
- Fetal demise
- PE
- Cardiac failure



- Fetal/neonatal Graves' disease (1-5%): tachycardia, goiter, advanced bone age, IUGR, craniosynostosis, cardiac failure, hydrops
- Tx: PTU (hepatotoxicity), Methimazole (aplasia cutis, esophageal atresia, choanal atresia), beta-blockers

PREGNANCY AND AUTOIMMUNE THYROID DISEASES III

- Hypothyroidism may cause infertility and abortions.
- Hypothyroidism in pregnancy: 3-5/1000
- Most common causes: Iodine deficiency (goiter) or Hashimoto's thyroiditis (autoimmune thyroiditis)
- Subclinical hypothyroidism: high **TSH**, but normal **fT4** levels: 2-2,5%
- **Anti-thyroid peroxidase (antiTPO) antibodies** are associated with pregnancy loss and PTD. They are (+) in 90% of cases with Hashimoto's thyroiditis.

PREGNANCY AND AUTOIMMUNE THYROID DISEASES IV

Adverse pregnancy outcomes in maternal hypothyroidism:

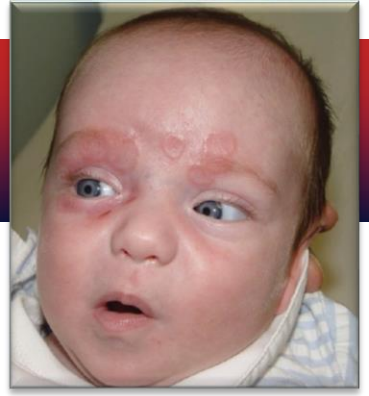
- Fetal distress
- PTD
- SGA
- Gestational HT and PE
- Ablatio placenta
- Perinatal morbidity and mortality
- Operative delivery
- Postpartum bleeding
- Neuropsychologic and cognitive disorders in the child

Hypothyroidism / Euthyroidism-antiTPO(+)-recurrent pregnancy loss→ Tx with Thyroxin

SLE I

- 1/1000 pregnancies
- Polyclonal B-lymphocyte activation → Antibodies against nuclear antigens and cell-surface antigens: ANA 96%/anti DNA 78% (+); aPL-Ab: 40% (+)
- Arthritis and skin problems are most common.
- Flares during pregnancy/puerperium (35-70%) ***Lupus flares and PE may be difficult to differentiate. Anti-DNA titers are increased and complement (C3,C4) concentrations are decreased during Lupus flares.
- Aspirin and/or LMWH are indicated in the presence of aPL-Ab or massive proteinuria in SLE.

SLE II



- SLE ←→ pregnancy loss, PE, IUBK, PTD
- **Anti-Ro (antiSS-A) ve/veya anti-La (antiSS-B)** antibodies (30%/15%)

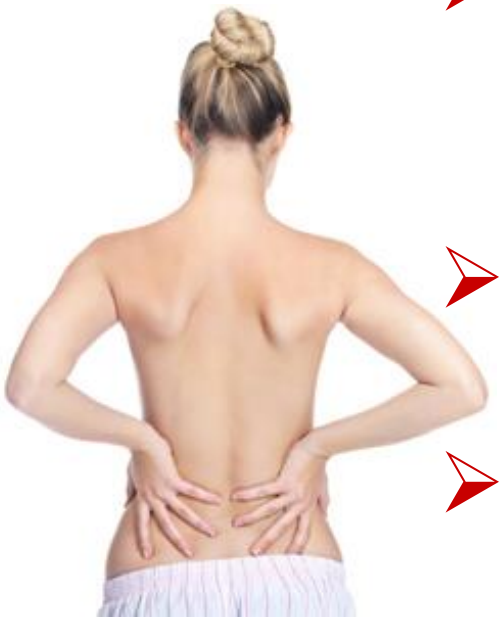
→ Neonatal Lupus Eritematozus (NLE) (%2): Congenital heart block (2%), skin problems

- Incomplete heart block diagnosed in the antenatal period may sometimes be reversed with steroids. Neonatal complete heart block is 20% mortal, 66% of neonates require pacemaker.

RHEUMATOID ARTHRITIS

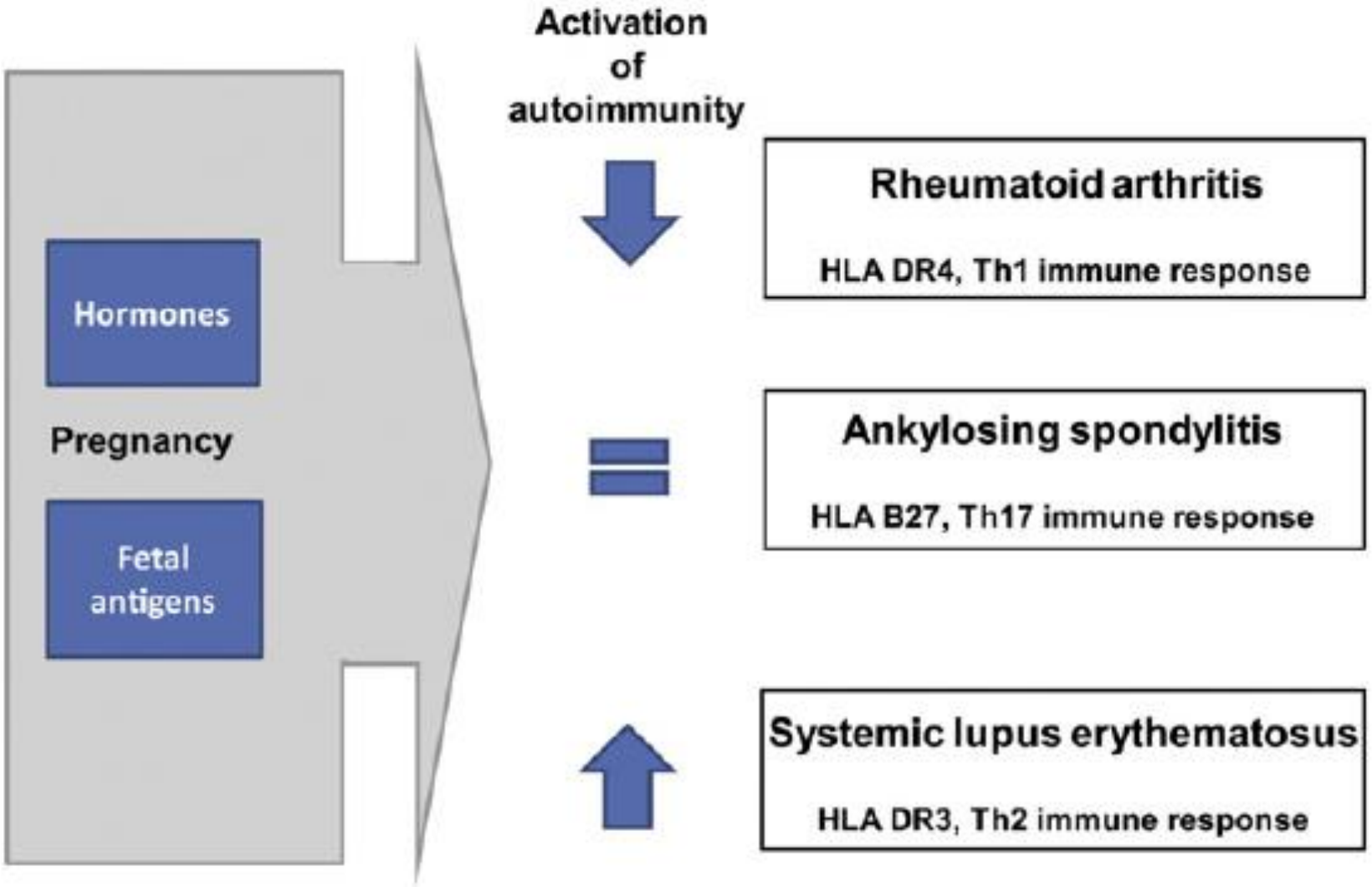
- 1/1000-1/2000 pregnancy
- Synovial joints and organs may be involved
- Associated with HLA D4
- CD4+ T cells are activated → cytokines and antibodies (RF) are released
- Immune complexes in synovial fluid and in the circulation
- Secondary Sjögren's syndrome (15%)
  → anti-Ro /anti-La may be (+)
- The disease usually improves during pregnancy (54-83%); after the delivery the symptoms may re-appear.
- Adverse fetal outcomes are rarely observed.

ANKYLOSING SPONDYLITIS



- Chronic arthritis predominanttly in the vertebral column and sacroiliac joints
- Associated with HLA B27
- Sometimes improved, sometimes worsened, sometimes (60%) no change in pregnancy
- No association with adverse pregnancy outcomes
- Increased symptoms after delivery: 50%

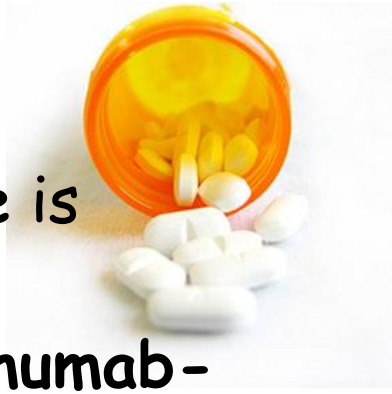
PREGNANCY AND AUTOIMMUNE DISORDERS



Østensen M,et al; 2012

TREATMENT OF AUTOIMMUNE DISORDERS DURING PREGNANCY

- Anti-inflammatory agents: Low dose **Aspirin** may be used, **Indometacin** and other NSAI agents are not preferred for long-term use. Glucocorticoids (**prednisolone**) may be used as an anti-inflammatory agent in SLE and rheumatoid arthritis.
- Immunesuppressants: **Hydroxychloroquine (Plaquenil), cyclosporin (Sandimmune), sulfasalazine (Salazopyrin), tacrolimus (Prograf)** may be used in low doses if necessary.
- Cytotoxic agents: Cyclophosphamide and methotrexate are contraindicated, **azathioprine** is relatively safer.
- TNFinhibitors: **Infliximab-Remicade/ Adalimumab-Humira/, Etanercept-Enbrel/ Certolizumab-Cimzia)**



TREATMENT OF AUTOIMMUNE DISORDERS DURING PREGNANCY (McCarthy F,et al; 2013)

		In pregnancy	In breast-feeding
Sulfasalazine	The use of sulfasalazine does not appear to increase risk of kernicterus. Used in treatment of RA. Crosses placenta	Category B early pregnancy Category D late pregnancy Yes (with folate supplementation pre-conception and throughout pregnancy)	Yes
TNF inhibitors including: Etanercept (soluble fusion protein), infliximab (chimeric monoclonal antibody) and adalimumab (humanized monoclonal antibody)	Very limited data and uncertainties regarding association with congenital abnormalities specifically the VACTERL association (Vertebral anomalies, Anal atresia, Cardiac defects, Tracheo-oesophageal fistula, oesophageal atraesia, Renal anomalies, and Limb dysplasia)	Category B	Not recommended (insufficient data)
Aspirin	Crosses placenta but no increase in risk of congenital defects	Category C (high-dose aspirin considered category D in 3rd trimester) Yes	Yes
Non-steroidal anti-inflammatory drugs	Avoid in third trimester due to risk of premature closure of ductus arteriosus (particularly indomethacin and ibuprofen)	Category C Yes	Yes
Glucocorticoids	Increased risk of orofacial clefts. May increase risk of PPROM, IUGR in the fetus and gestational diabetes, pregnancy induced hypertension, osteoporosis and infection in the mother	Category C (Prednisolone Category B) Yes	With caution (can discard breast milk expressed in hours after ingestion of glucocorticoids)

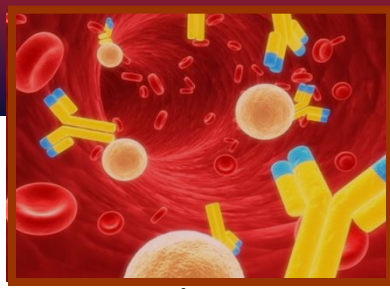
		In pregnancy	In breast-feeding
Cyclosporin	A calcineurin inhibitor. No increase in congenital malformations	Category C Yes	With caution. Small amounts in breast milk
Hydroxychloroquine	Traditionally an anti-malarial, used for preventing flare-ups in SLE. Crosses the placenta, but no adverse effects seen at doses used in these conditions	Category C Yes	Yes, infants exposed to only 2% of maternal dose
Tacrolimus	No increase in congenital malformations	Category C Yes with caution	With caution
Intravenous immunoglobulin	Crosses placenta after 30–32 weeks gestation and transport across placenta increases with increasing gestation	Category C	Not recommended
Azathioprine	AZA is metabolized to 6-MP in vivo. Fetus lacks enzyme to convert to active form Neonatal immunosuppression rare if dose <2 mg/kg and normal maternal white cell count	Category D Benefit appears to outweigh the risks	With caution, minimal amounts in breast milk
Cyclophosphamide	Alkylating agent Fetotoxic Teratogenic	Category D No, stop 3 months before conception	Not recommended
Retinoids	Teratogenic Fetotoxic	Category X No, discontinue at least 2 years prior to conception	Contraindicated
Methotrexate	Folate antagonist Embryotoxic in early pregnancy and causes skeletal abnormalities and cleft palate later in pregnancy	Category X No, discontinue at least 3 months prior to conception	Not recommended
PUVA	Systemic psoralen and ultraviolet A phototherapy	No FDA category Phototherapy alone appears safe Insufficient data regarding PUVA	Insufficient data

TREATMENT OF AUTOIMMUNE DISORDERS DURING PREGNANCY (Østensen M, Cetın I; 2015)

Table 3
Use of antirheumatic drugs during pregnancy.

Drugs to be discontinued before a planned pregnancy[a]	Drugs to be discontinued during the first trimester[b]	Drugs to be discontinued at the end of the second trimester[c]	Drugs that can be used throughout pregnancy
Methotrexate	Golimumab	Non-selective anti-inflammatory drugs[d]	Hydroxychloroquine, chloroquine
Leflunomide	Ustekinumab	Infliximab	Sulfasalazine
Mycophenolate mofetil	Belimumab	Adalimumab	Azathioprine
Cyclophosphamide		Etanercept	Cyclosporine
Rituximab			Tacrolimus
Abatacept			Prednisone, prednisolone
Tocilizumab			Low dose aspirin
			Paracetamol
			Intravenous immunoglobulin
			Certolizumab

ANTIPHOSPHOLIPID SYNDROME I
ACQUIRED THROMBOPHILIA



- Laboratory criteria:

aPL-Ab: (+) at least twice with 12 weeks apart

*Lupus antikoagulant,

*Anticardiolipin Ab (IgG/IgM),

*Anti-β2 glycoprotein I Ab (IgG/IgM)

- Clinical criteria:

DVT/TE or adverse pregnancy outcomes

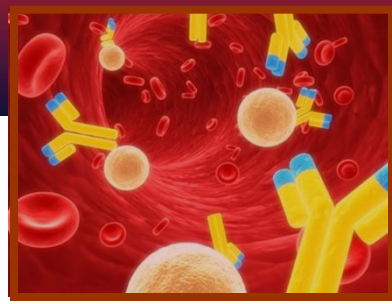
*pregnancy loss ≥10 wk,

*PTD <34 weeks due to PE, E or IUGR,

*Embryo loss ≥3 <10 weeks

Revised Sapporo criteriai; Sydney 2006

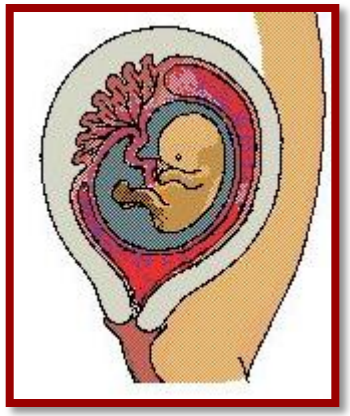
ANTIPHOSPHOLIPID SYNDROME II
ACQUIRED THROMBOPHILIA



- APS:

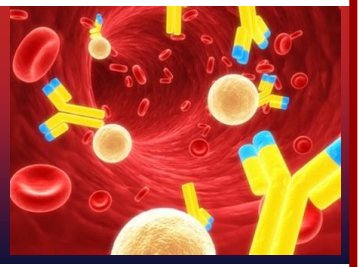
  Aspirin+LMWH during pregnancy (live-birth rate: 70-80%) and postpartum 6 weeks

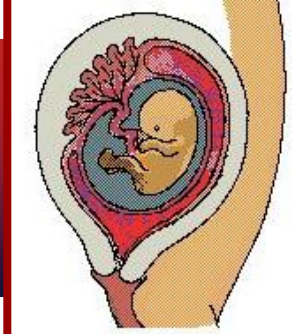
  Aspirin (80-100 mg): may be initiated preconceptionally, LMWH may be initiated when pregnancy test is (+).



- APL Ab (+) but not APS: Aspirin?

SUMMARY





- Pregnancy may affect the course of autoimmune disorders.
- Disorders like Rheumatoid Arthritis, with predominant joint involvement, few organ manifestations and few autoantibodies rarely impair pregnancy outcomes.
- aPL-Ab or APS increase the risk of abortions, PE, IUGR, fetal demise and PTD.
- Anti-Ro andAnti-La Ab may cause congenital Lupus and heart block.
- Presence of active disease at conception, renal involvement, (+) aPL-Ab are associated with adverse pregnancy outcomes.


NICE AND HEATHY DAYS...