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" YTP UPDATE 2020"

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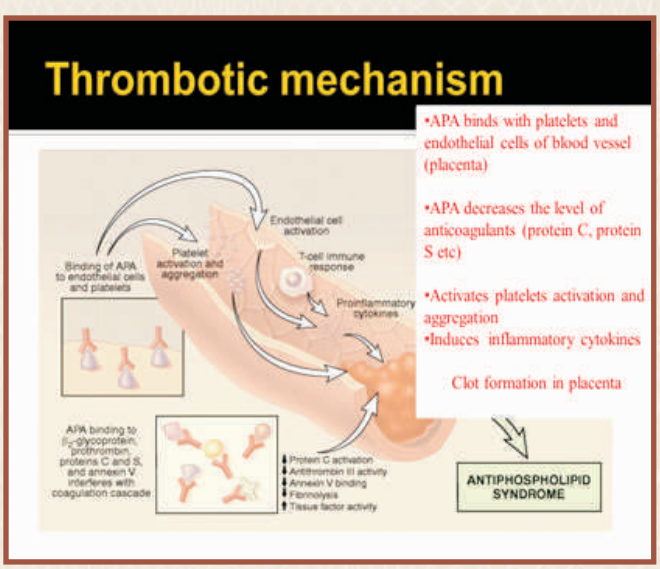
ROLE OF LMWH in RPL & RIF

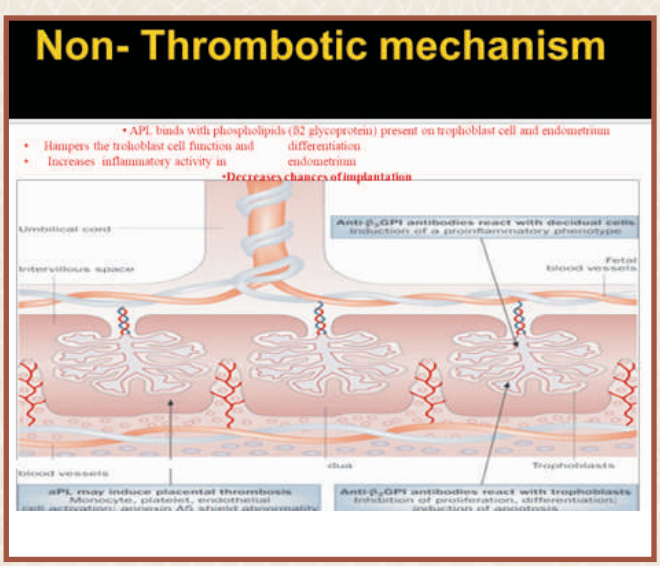
INTRODUCTION :

Clinically recognized pregnancy loss is common, occurring in approximately 15–25% of pregnancies. Recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies. It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more.
APS(Anti-Phospholipid Syndrome) is recognized as the most significant cause of RPL . In women with RPL the incidence of APS is between 20% and 40%.
Repeated Implantation Failure (RIF)- It is defined as failure of implantation in at least three consecutive IVF attempts, in which one to two embryos of high-grade quality are transferred in each cycle.
One of the important causes is Thrombophilia.
Patients with RIF have been shown to have an increased incidence of congenital and acquired thrombophilias

PATHOLOGY OF APS :

- Two mechanisms :
  - Thrombotic
  - Non thrombotic
- APS has also adverse effect on
  - Trophoblast function and differentiation,
  - Embryonic implantation,
  - Placentation





International Consensus Classification criteria for the antiphospholipid syndrome (APS)

APS is present if one of the following clinical criteria and one of the laboratory criteria are met.

Clinical criteria

1. Vascular thrombosis
2. Pregnancy morbidity
   a. One or more unexplained deaths of morphologically normal fetuses after the 10th week of gestation by ultrasound or direct examination of the fetus.
   b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia or recognized features of placental insufficiency.
   c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

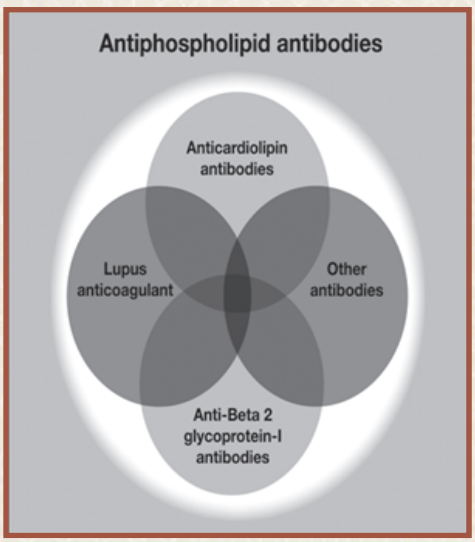
Laboratory criteria

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, or
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer (>40 GPL or MPL or > 99th percentile), on two or more occasions at least 12 weeks apart, or
3. Anti-b2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma (in titer greater than the 99th percentile), present on two or more occasions at least 12 weeks apart.

Practice Committee. Recurrent pregnancy loss. Fertil Steril 2012.

DIAGNOSTIC ASSAY :

- **APLA (Antiphospholipid Antibodies) test**
- **Activated Protein C resistance with factor V Leiden if abnormal,**
- **Prothrombin G20210A Polymorphism**
- **Protein C**
- **Protein S &**
- **Antithrombin (III)**



There are three primary classes of antibodies associated with the antiphospholipid syndrome : (1) anticardiolipin antibodies (aCL), (2) the lupus anticoagulant (LA) and (3) antibodies directed against beta-2-glycoprotein 1 (anti-b2GPI). Lupus antibody is the most powerful predictor of thrombosis and recurrent miscarriages. Anti-b2-glycoprotein- 1 antibodies are not associated with recurrent miscarriage in isolation; however, in combination with positive results for lupus anticoagulant (LA) and aCL, there is a high risk of obstetric complications.

GOALS OF TREATMENT

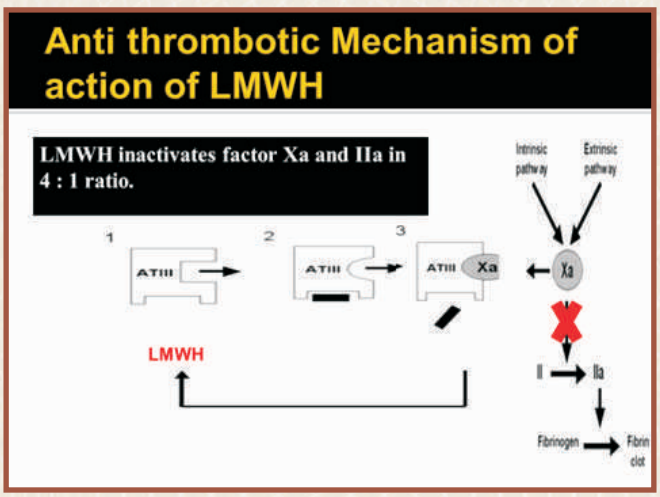
- To improve maternal and fetal-neonatal (newborn) outcomes by reducing the risks of the following complications such as
  - Maternal thrombosis,
  - Fetal loss,
  - Preeclampsia, placental insufficiency, and
  - Fetal growth restriction.
- To eliminate the risk of thromboembolism.

TREATMENT OPTIONS FOR THROMBOPHILIA

- Low dose aspirin
- Heparin
- Low molecular weight heparin (LMWH).

- LMWH has mainly two mechanisms by which it improves pregnancy outcome:

Anti thrombotic Mechanism of LMWH



Non thrombotic mechanism of action of LMWH

- Binds to antiphospholipid antibodies & inactivates them.
- Modulate trophoblast invasion
- Restores angiogenesis (blood vessel formation) in endometrium.
- Inhibits complement activation, thereby reduces recruitment of inflammatory cells, activation of tissue factor, and endothelial damage.

INDICATIONS

In ART :

- Patients of thrombophilia having **Repeated Implantation Failure(RIF)**
- Patients having **obstetric APS** undergoing ART
- Patients having severe **ovarian hyper-stimulation syndrome (OHSS)**

Recurrent pregnancy loss (RPL) in pregnancy associated with APS, Obstetric APS
Treatment of venous thromboembolism (VTE)

Investigational uses:

- **Empirical treatment** of repeated implantation failure
- For treatment of **inherited thrombophilia** associated pregnancy loss

LMWH DOSAGE

- Prophylactic dose:
  - Enoxaparin 40 mg subcutaneously every 24 hours.
- Therapeutic dose-
  - Enoxaparin 1 mg/kg subcutaneously every 12 hours, or enoxaparin 1.5 mg/kg/day subcutaneously.
- Enoxaparin dosing regimens in pregnancy are largely "borrowed" from nonpregnant regimens.#

#The journal of family practise, april 2004, volume 16, No. 4

Antenatal and postnatal prophylactic dose of LMWH recommended by the RCOG

Royal College of Obstetricians & Gynaecologists

- **Weight < 50 kg = 20 mg enoxaparin daily**
- **Weight 50–90 kg = 40 mg daily**
- **Weight 91–130 kg = 60 mg enoxaparin/daily**
- **Weight 131–170 kg = 80 mg daily**
- **Weight > 170 kg = 0.6 mg/kg/day enoxaparin**

Green-top Guideline No. 37a April 2015

Recommendation from ESHRE Guideline(2017) on the management of recurrent pregnancy loss :

Recommendations

For women who fulfill the laboratory criteria of APS and a history of three or more pregnancy losses, we suggest administration with low-dose aspirin (75 to 100 mg/day) starting before conception, and a prophylactic dose heparin (UFH or LMWH) starting at date of a positive pregnancy test, over no treatment.

Royal College of Obstetricians & Gynaecologists

Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium

Green-top Guideline No. 37a
April 2015

8.1 Low-molecular-weight heparin (LMWH)

LMWHs are the agents of choice for antenatal and postnatal thromboprophylaxis.

Doses of LMWH are based on weight. For thromboprophylaxis the booking or most recent weight can be used to guide dosing.

Monitoring of anti-Xa levels is not required when LMWH is used for thromboprophylaxis.

Dosage regimen in treatment of APS in pregnancy

Patients	Treatment
•Patients with APS without previous, thrombosis but had ➢Recurrent early (pre-embryonic or embryonic) miscarriage. ➢Fetal death (more than 10 weeks' gestation)	Prophylactic doses of heparin/LMWH and low-dose aspirin during pregnancy and 6 weeks of postpartum should be considered
•Patients with APS without previous thrombosis but had ➢Previously early delivery (<34 weeks gestation) due to severe preeclampsia or placental insufficiency	Low-dose aspirin and Prophylactic dose of UFH or LMWH

Dosage regimen in treatment of APS in pregnancy

Patients with APS with thrombosis	Low-dose aspirin and UFH or LMWH in therapeutic dose (1 mg/kg every 12 h subcutaneously, OR 1.5 mg/kg per day subcutaneously)

•**Started after documentation of fetal heart activity** in the early first trimester;

•**Stopped 24 hours before induction** or as soon as patient feels labor pain.

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th , 9TH edition)

Dose in repeated implantation failure (RIF) in ART

Patients with RIF	Treatment
Having APS History of hypercoagulability	•Prophylactic dose (40 mg/day) concomitant with gonadotropin administration. •Treatment should be stopped 24 hours before egg retrieval •Reinitiated the day after ovum pick-up.
Having thrombophilia No history of thrombotic events, Uneventful IVF treatments:	Start LMWH on the day of embryo transfer (ET)
Enoxaparin and aspirin may be continued upto 10–12 weeks of pregnancy or 34 weeks of gestation as per the practice of the clinician/ requirement of patient	

CONTRAINDICATIONS

- Active major bleeding
- Thrombocytopenia with a positive in vitro test for anti-platelet antibody in the presence of enoxaparin sodium
- Hypersensitivity to enoxaparin sodium

PRECAUTIONS – IN PATIENTS

- At risk of increased hemorrhage
- With bleeding diathesis, arterial hypertension or history of gastrointestinal ulceration, diabetic
- retinopathy, renal dysfunction, or hemorrhage
- History of heparin-induced thrombocytopenia
- Thrombocytopenia (reduced platelet counts)
- Pregnant women with mechanical prosthetic heart valves need more frequent monitoring and dosage adjustment
- With urgent case of delivery

ADVERSE REACTION

Generally well tolerate but most common adverse reactions are:

- Bleeding,
- Anemia,
- Thrombocytopenia,
- Elevation of serum aminotransferase,
- Diarrhea, and nausea

SAFETY OF ENOXAPARIN

- It does not cross placenta ,so it is safe during pregnancy.
- It is well tolerated
- Not associated with a clinically meaningful increase in the incidence of PPH.
- Incidence of thrombocytopenia and osteoprosis are less.
- ADMINISTRATION – : Subcutaneous, must not be administered as intramuscular injection.

USE OF ENOXAPARIN IN MANAGEMENT OF APS IN PREGNANCY IS RECOMMENDED BY

- Royal College of Obstetricians and Gynecologists (RCOG)
- American College of Obstetricians and Gynecologists (ACOG)
- American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
- British Journal of Hematology guideline