



How to treat MPNs with pregnancy

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Disclosure

- The author has no conflicts of interest to disclose concerning the presentation



Outline

- MPNs in AYA (age 15-39)
- R-IPSET
- Effect of ET to Pregnancy
- Effect of Pregnancy to ET
- Risk Factors in Pregnancy Complications
- Practical Guidelines: ET with Pregnancy
- High-risk pregnancy
- IFN Dose in ET with pregnancy



MPNs: ET



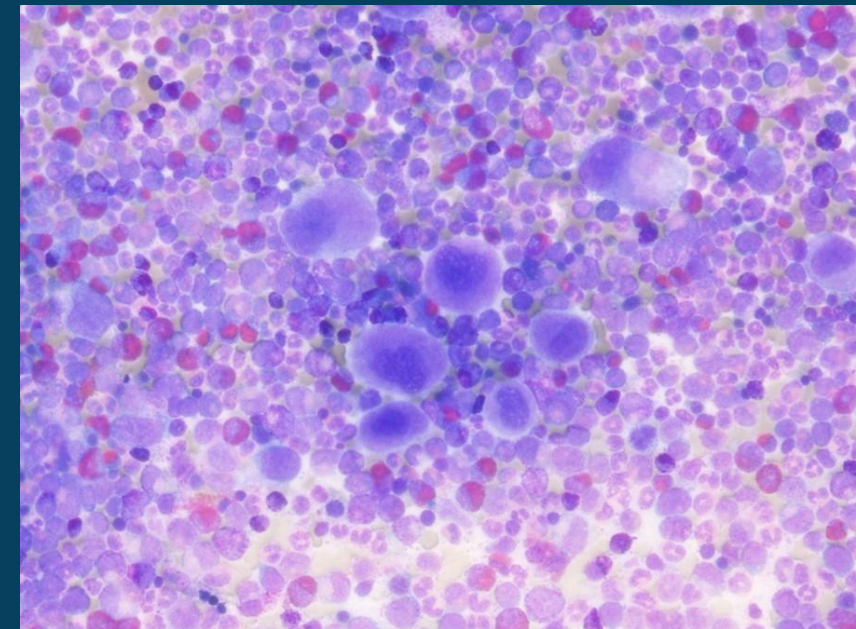
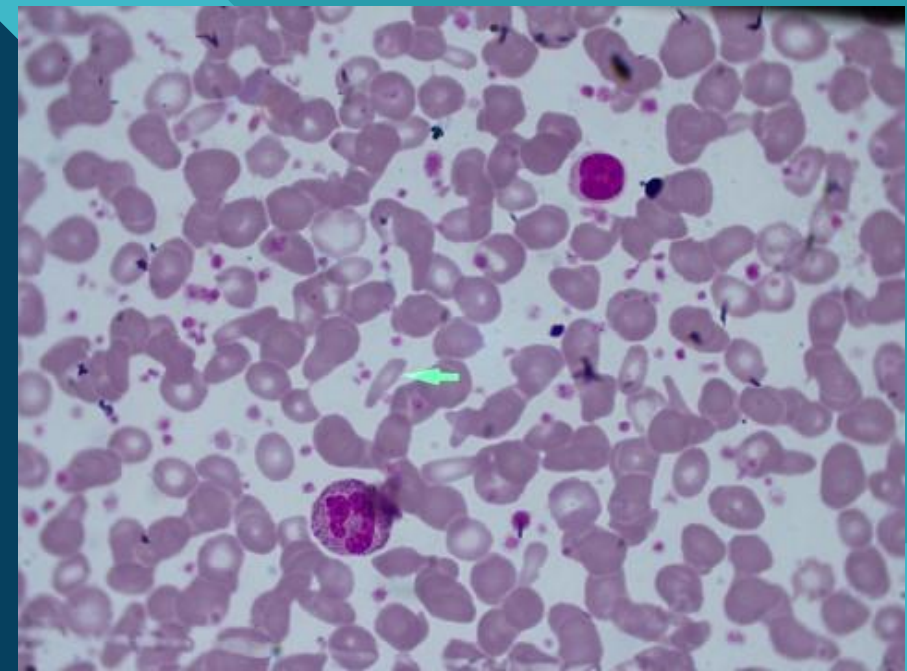
- Estimated annual incidence 0.65-2.5/100,000
- 20% ET patients Dx before age 40
- Prevalence MPNs in pregnancy 3/100,000 preg/year (ET 51-72%, CALR 11%)
- WHO classes all myeloproliferative neoplasms as blood cancers.
- Many people with MPNs feel well and only need gentle treatment.
- The disorders often develop slowly and progress slowly. Or they can remain stable for a while.

MPNs: Symptoms



- tiredness (fatigue)
- bruising or unusual bleeding
- getting more infections than usual
- blurred vision
- ringing in your ears
- digital ischemia
- night sweats
- itchy skin (pruritis)
- weight loss
- frequent headaches
- Asymptomatic but diagnosed after a routine blood test
- Thromboembolic

MPNs: ET



MYELOPROLIFERATIVE NEOPLASMS IN THE ADOLESCENT AND YOUNG ADULT (AYA) POPULATION

Adolescents and Young Adults (AYA), defined as between the **ages of 15 to 39 years**, encompass a unique population within the field of myeloproliferative neoplasms (MPN)

Most common MPN in AYA is **essential thrombocythemia**

MPN AYA demonstrate **female predominance**

Higher incidence of ***CALR* mutations**

High rates of venous thrombosis, particularly **splanchnic vein thrombosis**

Superior overall survival compared to older adults

If cytoreduction is required, **interferon is treatment of choice**

Special considerations for MPN AYA include **care during pregnancy**

Psychosocial burden remains area of concern for many AYA patients



R-IPSET (revised IPSET thrombosis categories)

Risk	H/O thrombosis	Age	JAK2V617F mutation	Treatment
Very low	No	≤ 60	unmutated	Observation or Low dose aspirin
Low	No	≤ 60	mutated	Low dose aspirin
Intermediate	No	> 60	unmutated	Low dose aspirin or Low dose aspirin with cytoreduction
High	Yes	or > 60	mutated	Cytoreduction with low dose aspirin



Case ET (1)

- 23-year-old woman (2548)
- H/O high platelet $1,400 \times 10^9/L$, bone marrow study and Dx ET
- No immediate Rx but F/U platelet $\rightarrow 1,900 \rightarrow 2,100 \rightarrow 2,300 \rightarrow 2,500 \times 10^9/L$
- S/S: Frequent headache, no DOE, no bleeding
- PE: no organomegaly
- Lab: Hct 35%, Hb 11.3 g/dL, WBC $12.6 \times 10^9/L$, PMN 70%, L 25%, M 4%, E 1%, platelet $2,375 \times 10^9/L$, MCV 62.1 (Homo E)
- BM: megakaryocytes markedly increased with giant, micromega, JAK2V617F not done (2548)
- R-IPSET: low to very low risk for thrombosis

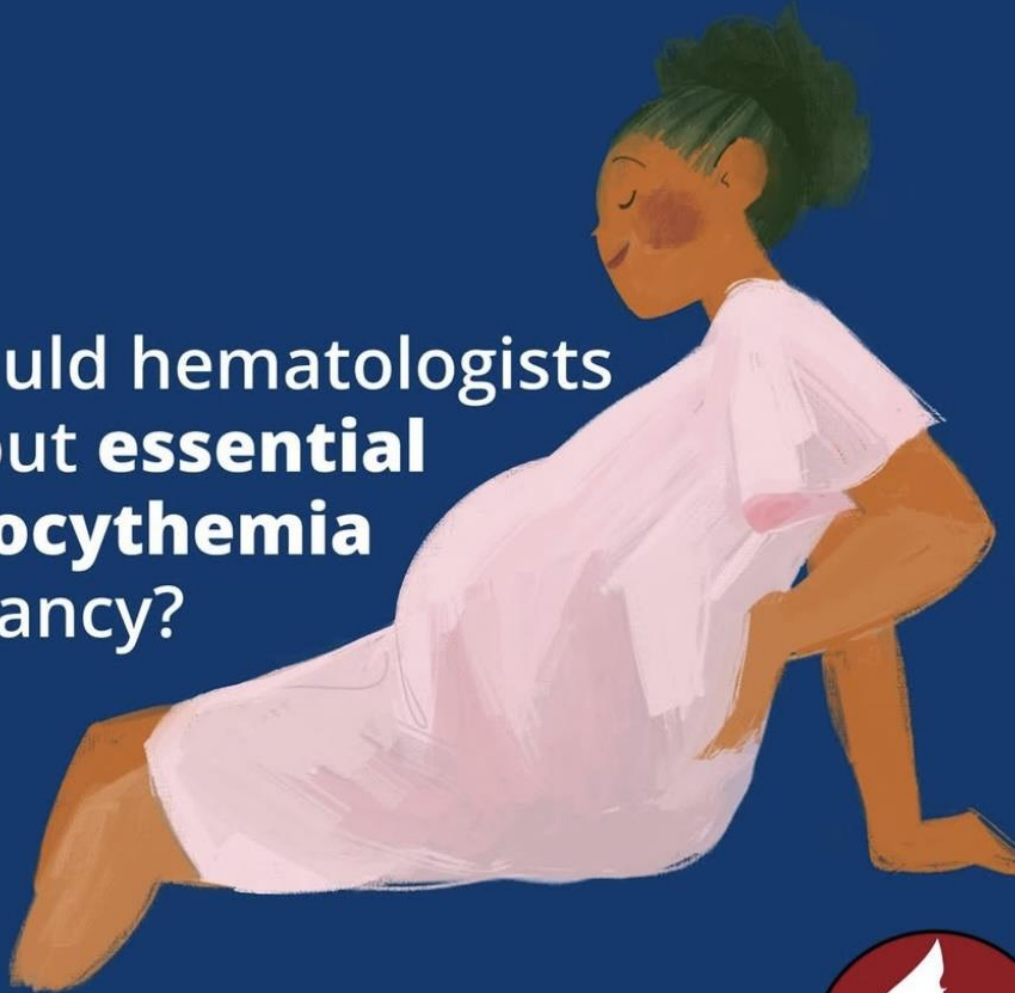


Case ET (2)

- Because of extreme thrombocytosis (platelet $2,375 \times 10^9/L$)
- Pt. received IFN alpha-2b 5MU SC x2/week for 9 weeks and add anagrelide 0.5 mg 1x3 → 2x2 with platelet 400-800 $\times 10^9/L$
- 2553, pt. informed pregnancy 4 weeks → D/C anagrelide and Rx peg IFN alpha-2a 135 mcg SC/week → q 2 weeks
- BASA 1x1
- No pregnancy complication with birth weight 2,700 gm.
- Peg IFN alpha-2a was extended to q 3-4 weeks → anagrelide 1x3
- Pt. lost F/U and had another healthy child. No cytoreduction Rx for 8+ years
- Platelet in 2561 900+ $\times 10^9/L$ – 1,000+ $\times 10^9/L$. On nature Rx, meditation



Why should hematologists
care about **essential
thrombocythemia**
in pregnancy?





Effect of ET to Pregnancy: Pregnancy complication 48.7%

- Spontaneous abortion (< 20 weeks) 26% vs 11% (normal preg)
- Stillbirth (> 20 weeks) 5% vs 0.5%
- Maternal thrombosis 2.4% (10 x normal)
- Maternal bleeding 5.8%
- Preeclampsia 3.3%
- Preterm delivery 7.4% vs 4%
- Low birth rate 10% vs 4%
- IUGR 2.5%
- Live birth rate 69% vs 80%

Pregnancy Complications



- Preeclampsia: new onset of HT $\geq 140/90$ x 2 times with proteinuria after 20 weeks gestation or other evidence of end-organ damage
- Gestational HT: new onset of HT $\geq 140/90$ and absence of preeclampsia Dx
- IUGR: fetal weight below 10th percentile for gestational age
- Preterm delivery: before 37 weeks gestation

First Trimester Miscarriage: Mechanism



- Placental micro-infarctions due to increased platelet number
- Platelet activation from more expression of P-selectin
- Platelet damage from autoantibodies
- Impact of JAK2V617F in pregnancy loss: controversial between studies



Risk Factors in Pregnancy Complications: Univariate Analysis

Factor	OR	p-value	90% CI
• JAK2 V617F positive	0.447	0.062	(0.224, 0.979)
• CALR positive	1.244	0.668	(0.370, 4.594)
• Years between diagnosis and pregnancy	0.985	0.904	(0.912, 1.060)
• Former Smoker	1.413	0.737	(0.436, 4.427)
• Cyto reduction prior to pregnancy	1.098	0.532	(0.260, 4.526)
• Prior Pregnancy Loss	2.626	0.040	(1.123, 5.579)
• Presence of medical comorbidity	0.772	0.811	(0.224, 2.554)
• Aspirin use during pregnancy	0.304	0.048	(0.102, 0.795)
• Maternal age	0.948	0.096	(0.867, 1.027)
• R-IPSET (High vs. Very Low)	1.923	0.513	(0.398, 13.339)
• Baseline platelet count	0.999	0.454	(0.996, 1.1001)
• Baseline hemoglobin	0.576	0.073	(0.279, 0.976)
• Baseline WBC	0.943	0.666	(0.607, 1.340)



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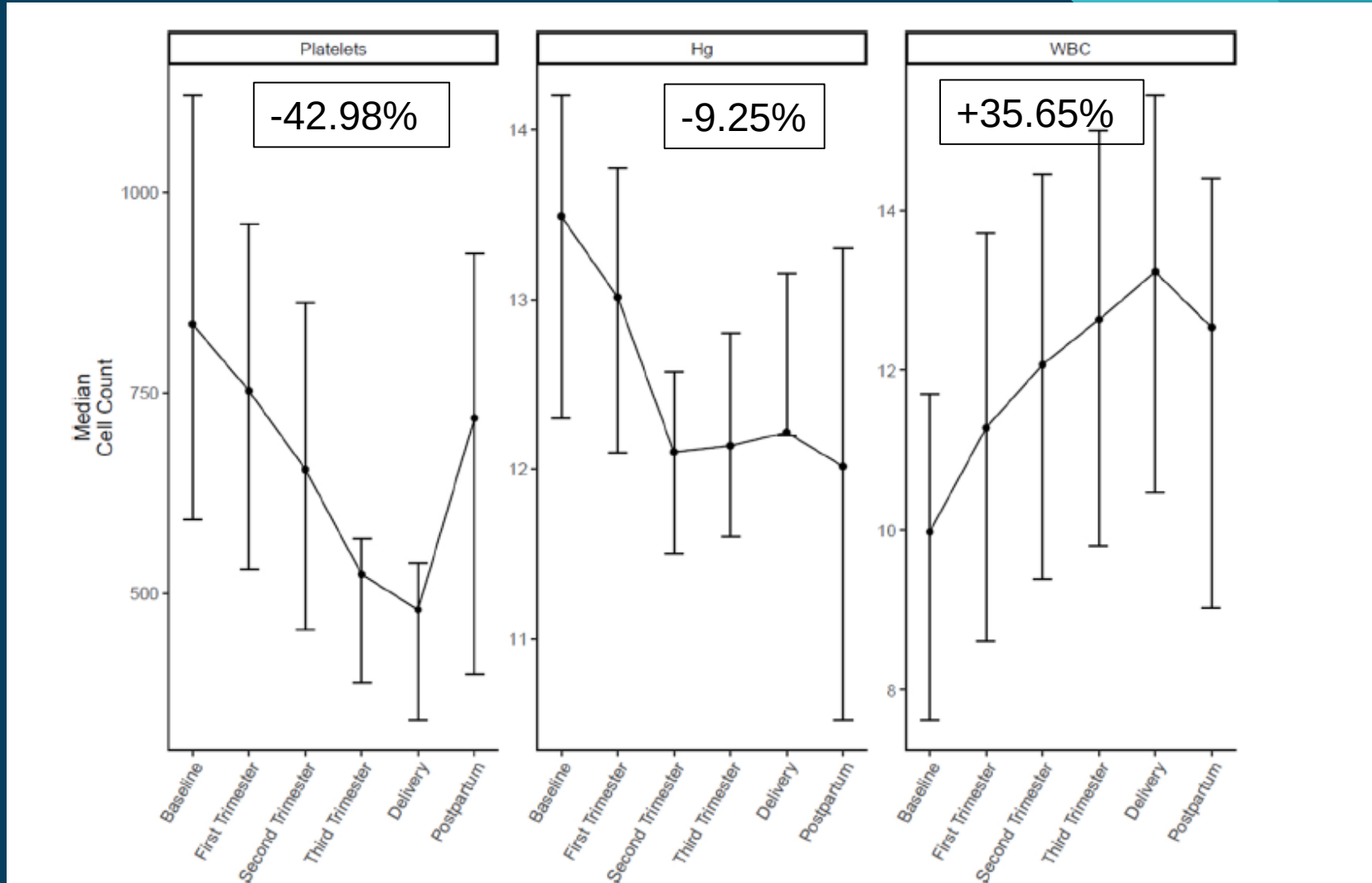


Risk Factors in Pregnancy Complications: Multivariate Analysis

Factor	OR	p-value	90% CI
• Prior Pregnancy Loss	3.86	0.012	(1.492, 9.147)
• Aspirin use during pregnancy	0.29	0.014	(0.118, 0.658)

- A woman with ET with an uncomplicated pregnancy has a probability of 0.367 (90 % CI 0.281, 0.558) for a subsequent complication in her next pregnancy
- In contrast, a woman with a complicated pregnancy has a probability of 0.594 (90 % CI 0.469, 0.746) for a subsequent complication

Effect of Pregnancy to ET: Gestational Cell Count Trends





Effect of Pregnancy to ET: Platelet Count

- The average platelet decline was $336 \times 10^9/L$ (90 % CI 12.3–393.9).
- ET women with a greater decline in platelets during pregnancy were less likely to suffer a pregnancy complication ($p = 0.083$).
- The mean change in baseline or first trimester to delivery platelet count was $-89.71 \times 10^9/L$ in women with complications compared to $-292.81 \times 10^9/L$ in women without complications.



Effect of Pregnancy to ET: Platelet Count ↓

- Dilutional effect
- Suppression of clonal hematopoiesis by secretion of interferon-like substances from the placenta
- Increased estrogen signaling → induce apoptosis in JAK2+ hematopoietic stem cells



Practical Guidelines: ET with Pregnancy (1)

Before Pregnancy

- Not ready: contraception
 - Avoid estrogen-containing pills (VTE risk 23% vs 7% non-estrogen)
 - Suggest progesterone-only pill, implant, injection or IUD
- Ready:
 - Stop HU, anagrelide (3- 6 month-washout) → switch to IFN alpha when being pregnant
 - Consultation with hematologist and high-risk obstetrician
- Ready: but having infertility → IVF, estrogen for ovulation
 - LMWH 40 mg SC/day in first 12 weeks



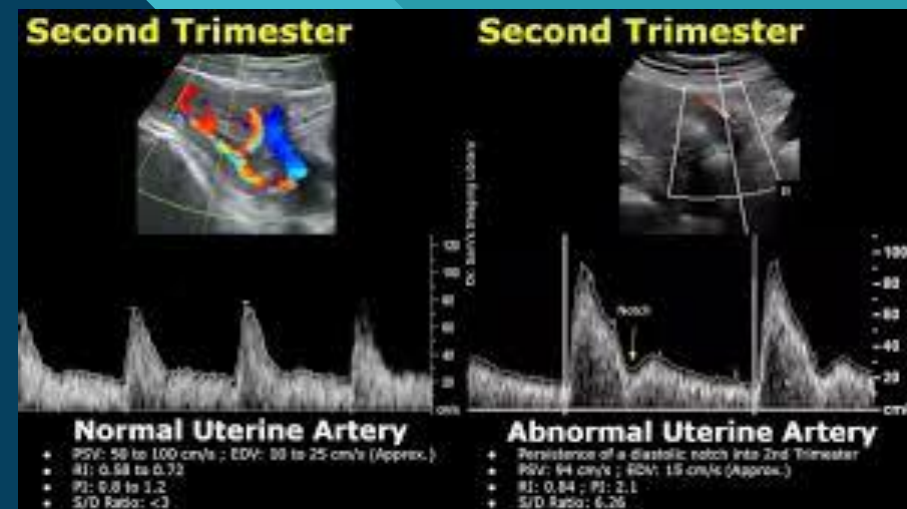
Practical Guidelines: ET with Pregnancy (2)

During Pregnancy

- Daily low dose aspirin 81 mg/day
- Monitor blood counts every 2 months
 - Increase frequency to monthly if platelet counts do not decline as expected (average 40 % decline by delivery)
 - Ristocetin cofactor testing and assessment of bleeding risk if platelets $>1,000 \times 10^9/L$
- Increased vigilance and consideration of step-up therapy with IFN alpha/LMWH prophylaxis in high-risk situations
 - Prior history of thrombosis or hemorrhage
 - Two or more hereditary thrombophilia factors
 - History of prior pregnancy complications
- Standard fetal assessment: U/S & uterine artery doppler scanning between 20-26 weeks
- At delivery: stop aspirin 1 week prior to delivery

High-risk pregnancy (although Low-risk IPSET)

- Extreme thrombocytosis $> 1,500 \times 10^9/L$
- Previous venous or arterial thrombosis
- Previous bleeding from PV or ET
- Previous pregnancy complication (only 1)
 - ≥ 1 unexplained death in normal looking fetus age ≥ 10 weeks
 - ≥ 1 preterm delivery in normal looking fetus age < 34 weeks caused by
 - Severe preeclampsia or eclampsia
 - Placental insufficiency
 - ≥ 3 consecutive unexplained miscarriage (spontaneous abortion) age < 10 weeks
 - unexplained intrauterine growth restriction
 - Antepartum or postpartum bleeding required transfusion
 - Abnormal uterine artery from Doppler at 20 weeks (mean pulsatility index > 1.4): blood is having to work harder to flow to the uterus (high resistance pattern),





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IFN for cytoreduction



Cytoreductive Rx in MPNs (1)

- HU: inhibit ribonucleotide reductase
 - embryotoxic/teratogenic effects.
- Anagrelide: imidazoquinazolin
 - inhibition of megakaryocytes differentiation
 - 0.5 mg x bid-qid, C/I pregnancy
 - Cross placenta → fetal thrombocytopenia
 - Rx during pregnancy → not a reason to terminate pregnancy
 - Breast-feeding should be D/C during Rx



Cytoreductive Rx in MPNs (2)

- IFN alpha
 - NonPeg, Peg, Ropeg
 - Anti-proliferative effects on megakaryocyte
 - No mutagenic or teratogenic
 - Induce molecular response
 - One study: IUGR, thrombocytopenia, neonatal drug-induced lupus
- Ruxolitinib
 - FDA, EMA approved for PV having inadequate response to HU
 - Nonteratogenic but causing low fetal weight in animal studies. C/I pregnancy



IFN Dose in ET with pregnancy

- PegIFN alpha-2a (Pegasys) start 45 mcg SC/week and increase 45 mcg/2 weeks, max. dose 180 mcg/week → q 2-4 weeks
- RopegIFN alpha-2b (Besremi) 100 mcg SC q 2 weeks
- Bioferon 3 MU SC OD x 3-5/week
- Aim: minimize dose to keep Platelet $< 600 \times 10^9/L$, in PV keep Hct $< 45\%$
- Plateletpheresis in cases refractory to IFN
- AEs: flu-like, musculoskeletal, endocrine, psychiatric, autoimmune

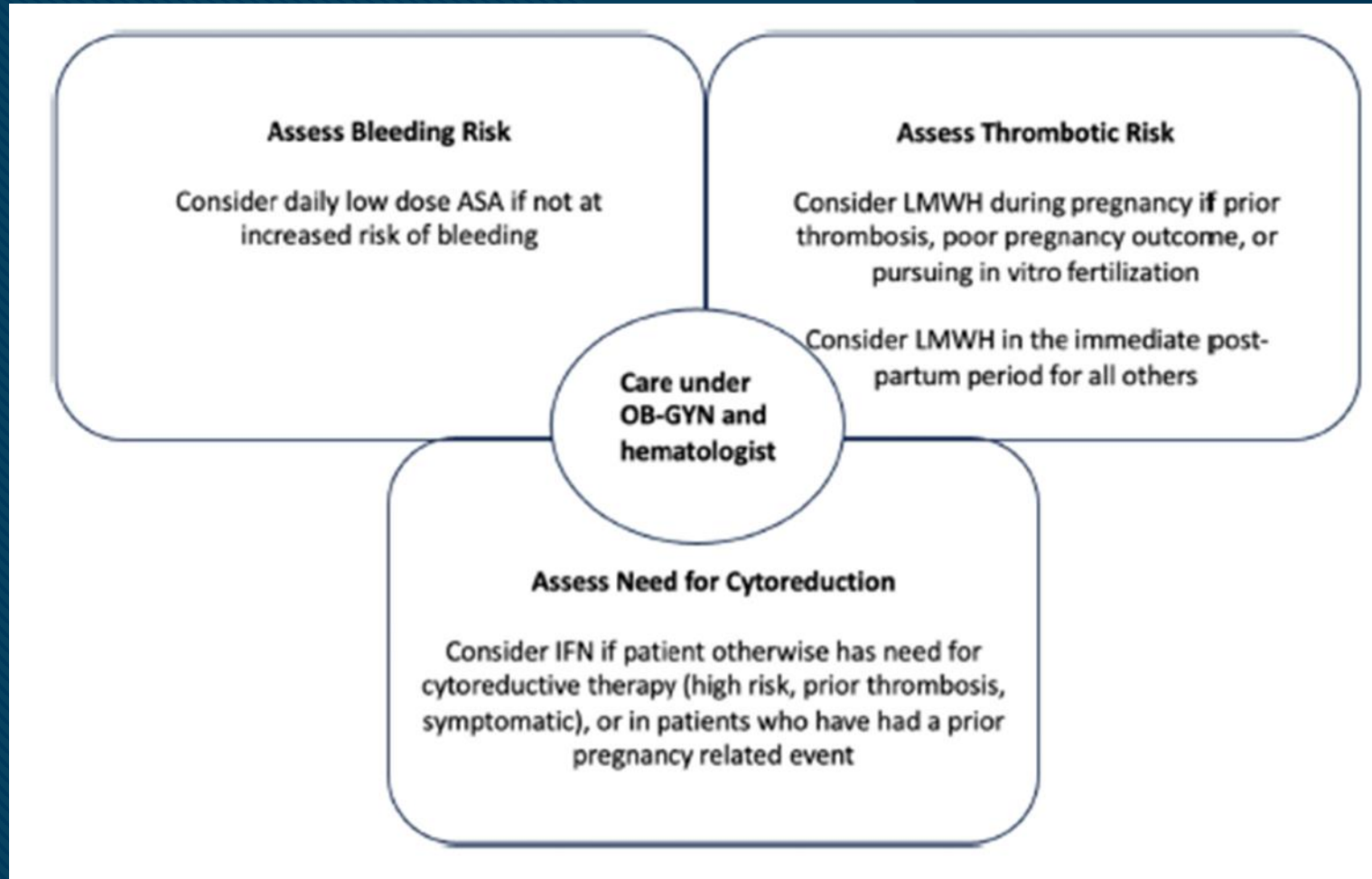


Practical Guidelines: ET with Pregnancy (3)

After Pregnancy

- Continued aspirin use 81 mg/day
- Consider LMWH prophylaxis 40 mg/day for 6 weeks postpartum
- Breastfeeding is contraindicated if cytoreduction needed, although interferon is likely safe for lactation

Treatment considerations during pregnancy for MPNs



Quiz time!

Which of the following is TRUE about Essential Thrombocythemia in pregnancy?

- A. ET always causes pregnancy complications.
- B. Women with ET should avoid aspirin during pregnancy.
- C. With proper management and monitoring, many women with ET can have successful pregnancies.
- D. ET temporarily disappears during pregnancy due to plasma volume expansion.



Guidelines for the Diagnosis
and Management of

MYELOPROLIFERATIVE NEOPLASMS (MPN) 2023



แนวทางเวชปฏิบัติสำหรับการวินิจฉัยและรักษา

Myeloproliferative Neoplasms (MPN) 2566

- Polycythemia Vera (PV)
- Essential Thrombocythemia (ET)
- Primary Myelofibrosis (PMF)
- Stem Cell Transplantation in Myelofibrosis

จัดทำโดย

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