GIORNATE EMATOLOGICHE VICENTINE

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Le neoplasie mieloproliferative e la donna

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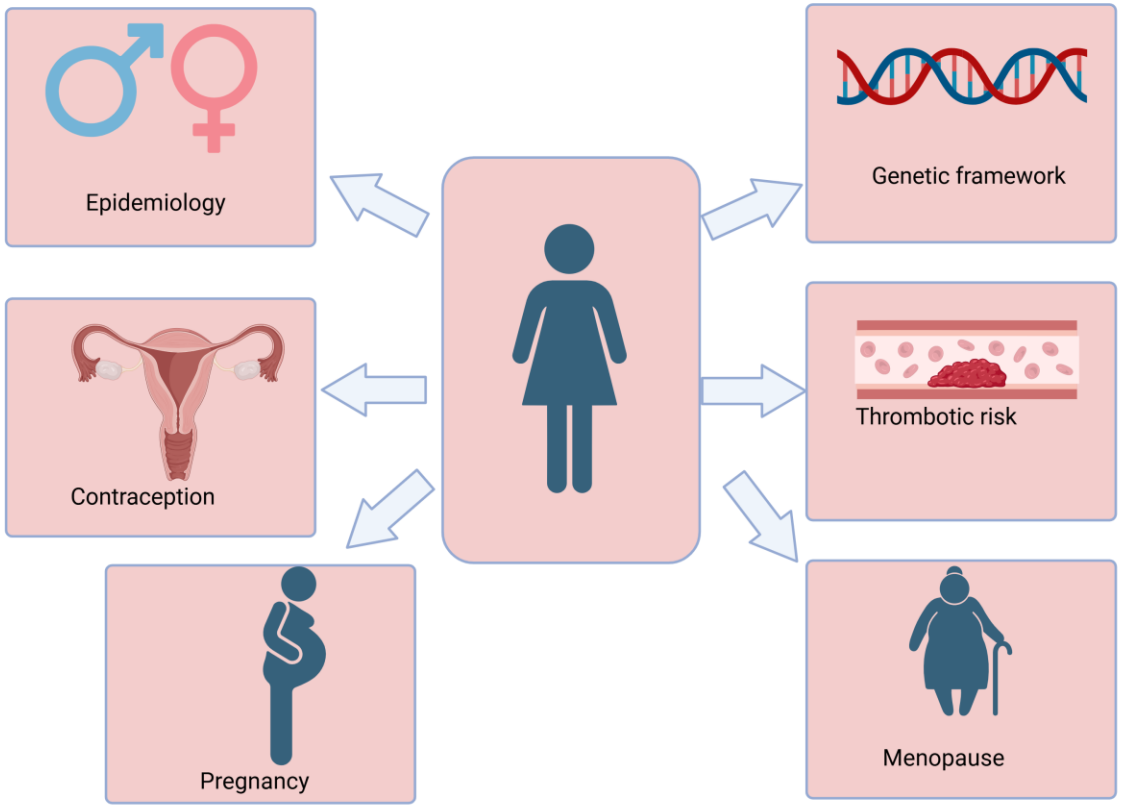
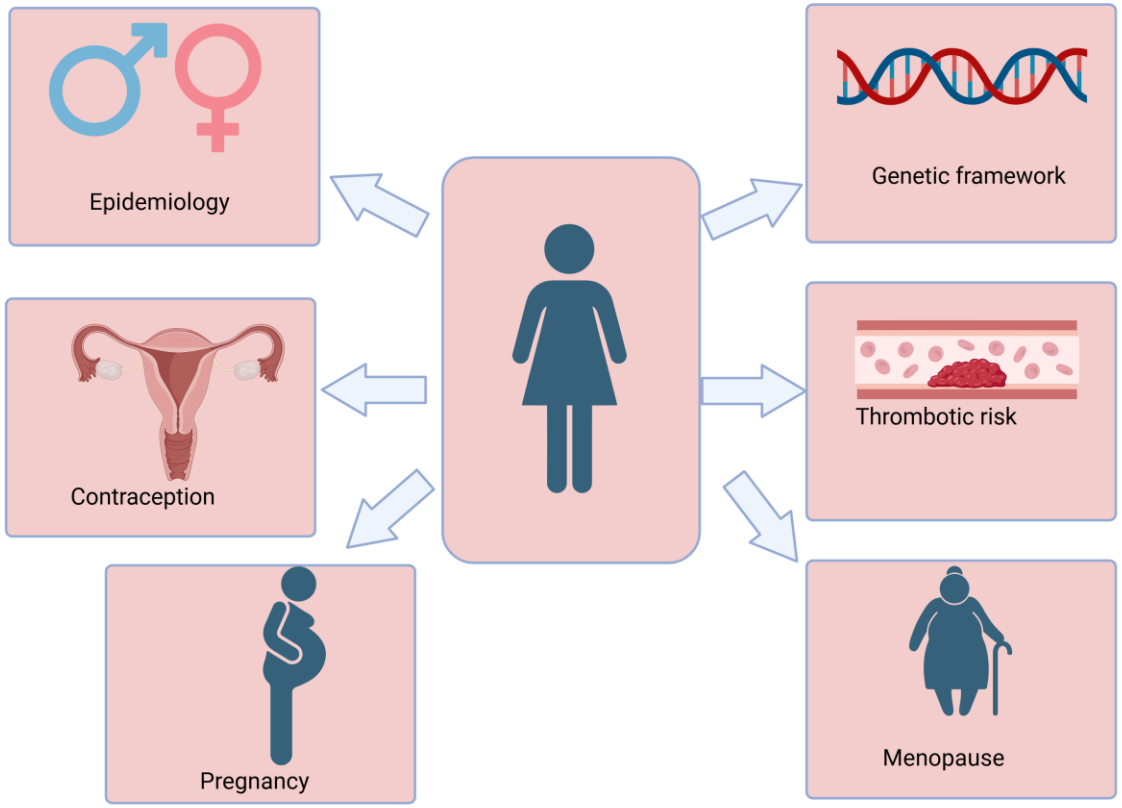

Epidemiology
Genetic framework
Contraception
Thrombotic risk
Pregnancy
Menopause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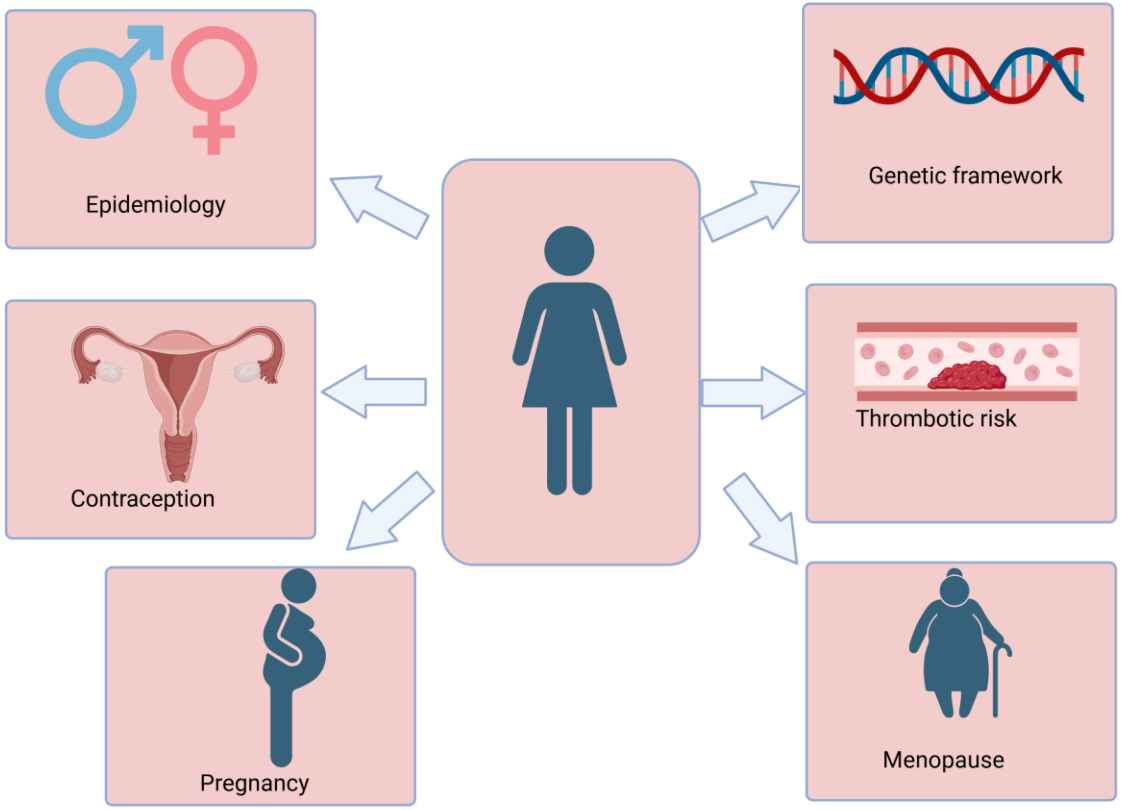
Epidemiology

- Distribution of MPN is unbalanced between sexes
- The incidence of ET is higher in women
- The incidence of PV and PMF is higher in men

Hultcrantz M, et al. J Intern Med. 2020 Apr;287(4):448-454.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Genetic framework

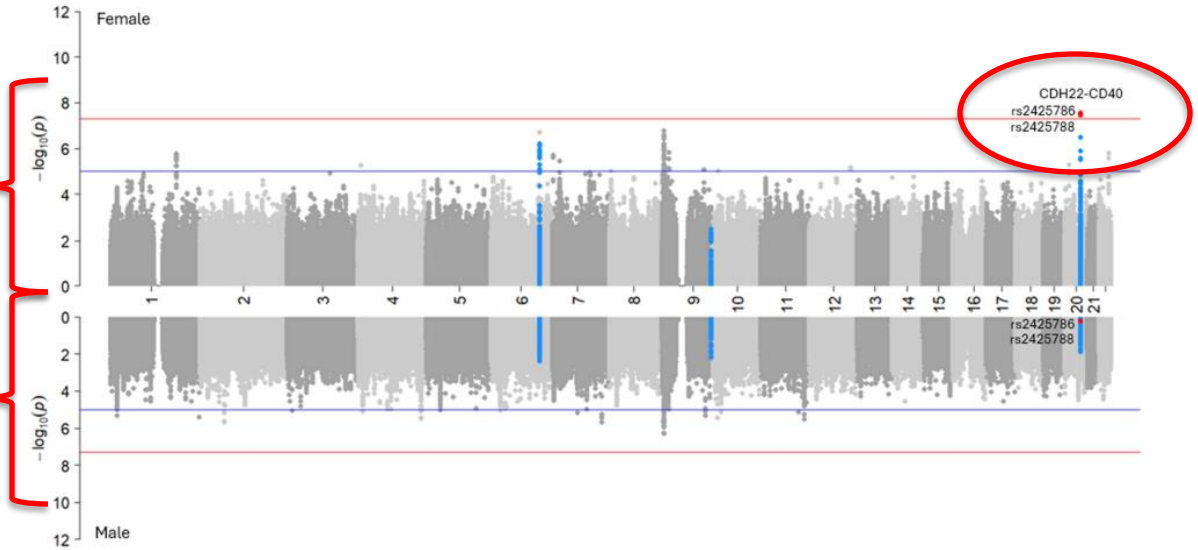
- *JAK2*/*CALR*/*MPL* mutations are equally distributed among sexes but triple negative cases are more frequent in women
- Women have lower *JAK2* V617F VAF and slower allele burden increase
- Women have fewer acquired somatic mutations and lower frequency of high-risk mutations

Karantanos T, et al. Blood Adv. 2020 Jun 23;4(12):2567-2576

Female

Male

Supplementary Figure 4. Genome-wide association of ET versus PV stratified by sex



Tapper, et al. Blood 2025 Sep 30; Epub ahead of print

GENETIC DETERMINANTS OF MPN SUBTYPE

Context of Research

Some patients who acquire *JAK2* V617F develop polycythemia vera but others develop essential thrombocythemia. The reason for this phenotypic difference is incompletely understood

Aim of This Study

To identify genetic variants that influence myeloproliferative neoplasm (MPN) phenotype, including variants that have gender-specific effects

Findings

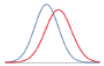
Genetic characterisation

- SNP array genotyping
- Imputation

Genome-wide association analyses

- ET versus PV
- ET versus controls
- PV versus controls

Polygenic Risk Score (PRS)



- Optimised for ET and PV

Female-specific association for variants within:

- *CDH22* (ET versus PV $P_{meta} = 2.67 \times 10^{-8}$)
  - Reduced ET risk ($P_{meta} = 7.82 \times 10^{-5}$, OR = 0.75)
  - Elevated PV risk ($P_{meta} = 0.0006$, OR = 1.30)
- eQTL for increased expression of *CD40* ($P = 3.80 \times 10^{-7}$)

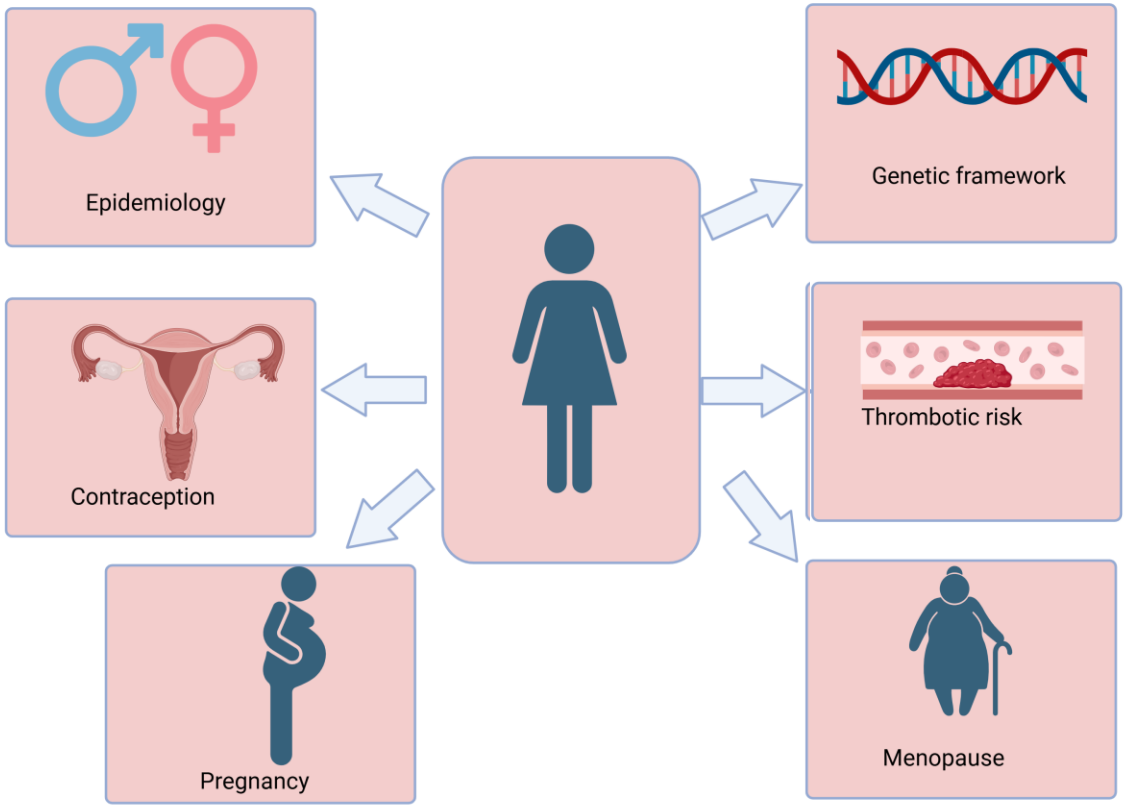
PRS constructed from 48 SNPs in 31 independent loci

- Optmised PRS show stronger associations with ET and PV versus PRS based on platelets and red blood cell traits

Conclusion: Multiple germline variants influence MPN phenotype, including a novel female-specific association with *CDH22/CD40*.

*Tapper et al. DOI: 10.xxxx/**blood**.2025xxxxxx*

Tapper, et al. Blood 2025 Sep 30; Epub ahead of print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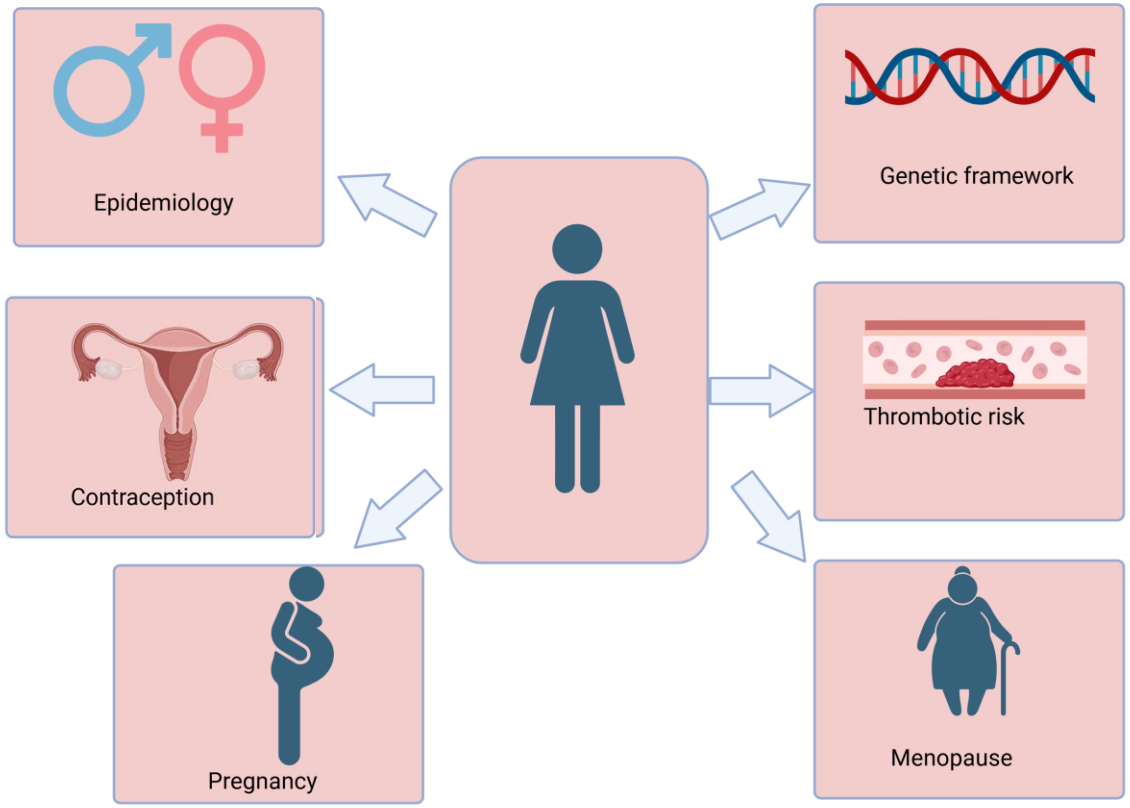
Thrombotic risk

- VTE are more common in females subjects
- Splanchnic vein thromboses are more frequent in women

Karantanos T, et al. Blood Adv. 2020 Jun 23;4(12):2567-2576
Colaizzo D, et al. Thromb Res. 2011 Sep;128(3):233-6.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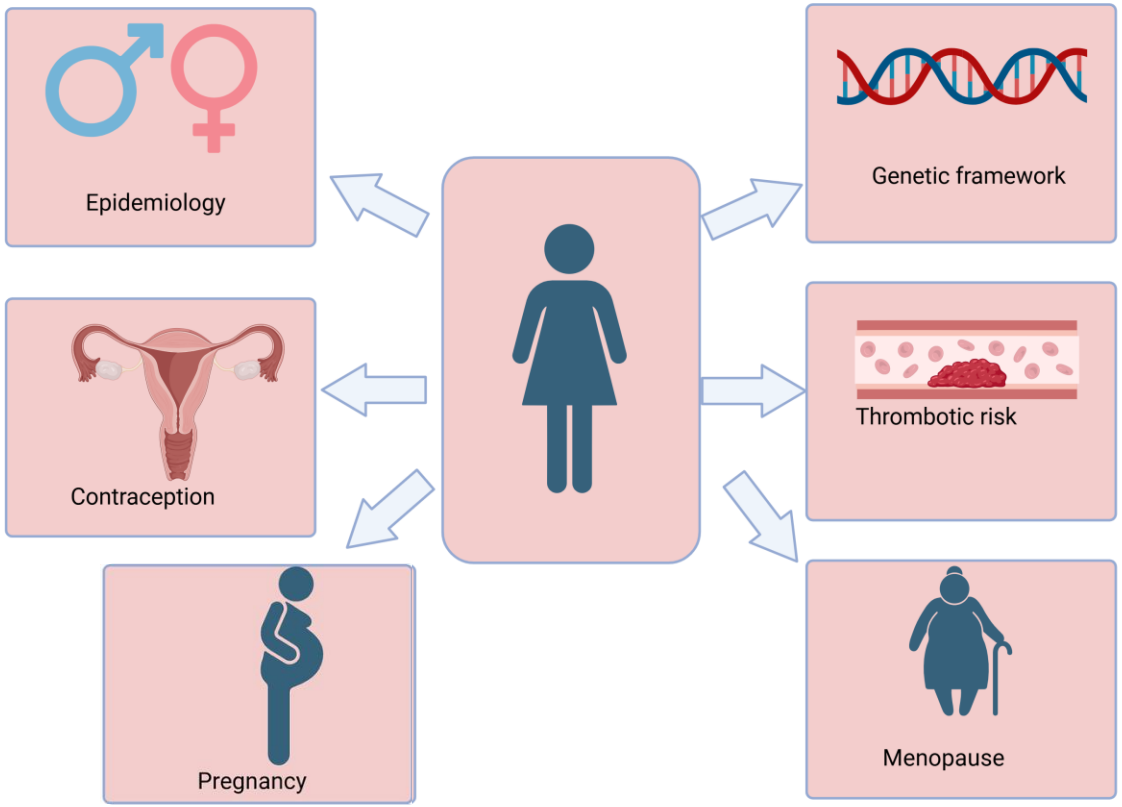
Contraception (OCP=oral contraceptives)

- 3-fold increased risk of overall venous thrombosis in OCP users compared with nonusers (23% vs. 7%)
- 5-fold increased risk of splanchnic venous thrombosis (15% vs. 3%) in OCP users compared with nonusers
- Recommend avoidance of estrogen-based contraception in favor of alternatives-progesterone-only pill, implant, depot, IUD or barrier methods.

Gangat N, et al. Cancer. 2006 Jun 1;106(11):2406-11.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Pregnancy

- Young women of childbearing potential constitute around 10% of newly diagnosed MPN cases
- Women with MPN (15-44 years) have a 22% lower childbirth rate compared to the control population: not reduced in ET (HR:1.02) but reduced in PV (HR:0.5) and PMF (HR:0.45)

Szuber N, et al. Am J Hematol. 2018 Dec;93(12):1474-1484
Landtblom AR, et al. Leukemia. 2024 May;38(5):1081-1085

Pregnancy in ET

	Mayo Clinic study [74]	Italian study [77]	Italian study [78]	Partners Boston study [75]	Combined results
Women/pregnancy, *n*	100/200	94/155	92/122	52/121	338/598
Genetics, *n/n evaluable* (%)					
JAK2 mutated	44/86 (51)	59/94 (63)	16/37 (43)	29/52 (56)	148/269 (53)
CALR mutated	21/76 (28)	19/94 (20)	—	6/52 (12)	46/222 (21)
MPL mutated	0/76 (0)	2/94 (2)	—	0/52 (0)	2/222 (1)
Triple negative	4/76 (5)	14/94 (15)	—	4/52 (8)	22/222 (9)
Treatment, *n/n evaluable* (%)					
Aspirin	135/200 (68)	—	93/122 (76)	62/107 (51)	290/429 (65)
LMWH (antepartum)	19/200 (10)	—	19/93 (20)	10/84 (12)	48/377 (14)
LMWH (postpartum)	29/200 (15)	—	—	17/84 (20)	46/284 (18)
Interferon	17/200 (9)	—	20/122 (16)	2/121 (2)	39/443 (10)
No treatment	52/200 (26)	—	—	—	52/200 (26)
Live birth, *n* (%)	144 (72)	106 (68)	92 (75)	84 (69)	426/598 (71)
Fetal complications, *n* (%)					
Fetal loss	56 (28)	46 (30)	30 (25)	39 (32)	171/598 (29)
First-trimester loss	51 (26)	37 (24)	19 (16)	—	107/477 (22)
Spontaneous	48 (24)	37 (24)	19 (16)	32 (26)	136/598 (23)
Elective	3 (2)	—	—	4 (3)	7/321 (3)
Second-trimester loss	3 (2)	6 (4)	7 (6)	—	16/477 (6)
Third-trimester loss	0 (0)	3 (2)	—	—	3/355 (2)
Stillbirth	2 (1)	3 (2)	4 (3)	1 (0.8)	10/598 (2)
Preterm birth	6 (3)	20 (13)	12 (10)	9 (7)	47/598 (8)
IUGR	5 (3)	13 (8)	2 (2)	3 (3)	25/598 (4)
Maternal complications, *n* (%)	26 (13)	18 (12)	10 (8)	15 (12)	69/598 (11)
Thrombosis	2 (1)	—	5 (4)	3 (3)	10/343 (3)
Major bleeding	13 (7)	—	1 (1)	7 (6)	21/343 (4)
Pre-eclampsia	11 (6)	—	3 (3)	4 (3)	18/343 (4)
Placental abruption	1 (0.5)	—	1 (1)	0 (0)	2/343 (0.5)
Gestational hypertension	—	—	—	1 (1)	1/121 (1)

Szuber N, et al. Am J Hematol. 2025 Jun;100 Suppl 4(Suppl 4):74-87.

Pregnancy in ET

- Prior pregnancy loss is the most important predictor of subsequent fetal loss in ET
- Role of driver mutation on fetal-loss and pregnancy-related complications is conflicting:
  -Mayo experience: *JAK2* does not increase the risk
  -PV experience: *JAK2* is associated with increased risk, in particular with late pregnancy losses; *CALR* mutations are associated with a trend to a better outcome
- The protective role of ASA against fetal loss confirmed in several studies

Gangat N et al. Eur J Haematol. 2009 May;82(5):350-3
Passamonti F, et al. Blood. 2007 Jul 15;110(2):485-9
Rumi E et al. Haematologica. 2015 Nov;100(11):e443-5.

Management recommendations fo pregnancy in ET: before

- Careful preconception counselling
- Integrated care by hematology and obstetrics teams
- Check thrombophilia and cardiovascular risk factors
- Hydroxyurea and warfarin are teratogenic: avoid in young women contemplating a future pregnancy

Robinson S et al. Blood. 2024 Feb 29;143(9):777-785
Gangat N, et al. Am J Hematol. 2021 Mar 1;96(3):354-366
How J et al. Hematology Am Soc Hematol Educ Program. 2024 Dec 6;2024(1):541-546.

Management recommendations fo pregnancy in ET: during

- Low risk ET: aspirin alone (avoid if PLT>1.000x109/l or AvWS)
- High risk: cytoreductive therapy (INF-α 45 mcg/sett) in addition to aspirin
- LMWH in patients with history of venous thrombosis (stop 24 hours prior to delivery via Cesarean section)

Robinson S et al. Blood. 2024 Feb 29;143(9):777-785
Gangat N, et al. Am J Hematol. 2021 Mar 1;96(3):354-366
How J et al. Hematology Am Soc Hematol Educ Program. 2024 Dec 6;2024(1):541-546.

Management recommendations fo pregnancy in ET: after

- LMWH for 6 weeks after delivery
- Breastfeeding: LMWH, aspirin, and IFN preferred agents

Robinson S et al. Blood. 2024 Feb 29;143(9):777-785
Gangat N, et al. Am J Hematol. 2021 Mar 1;96(3):354-366
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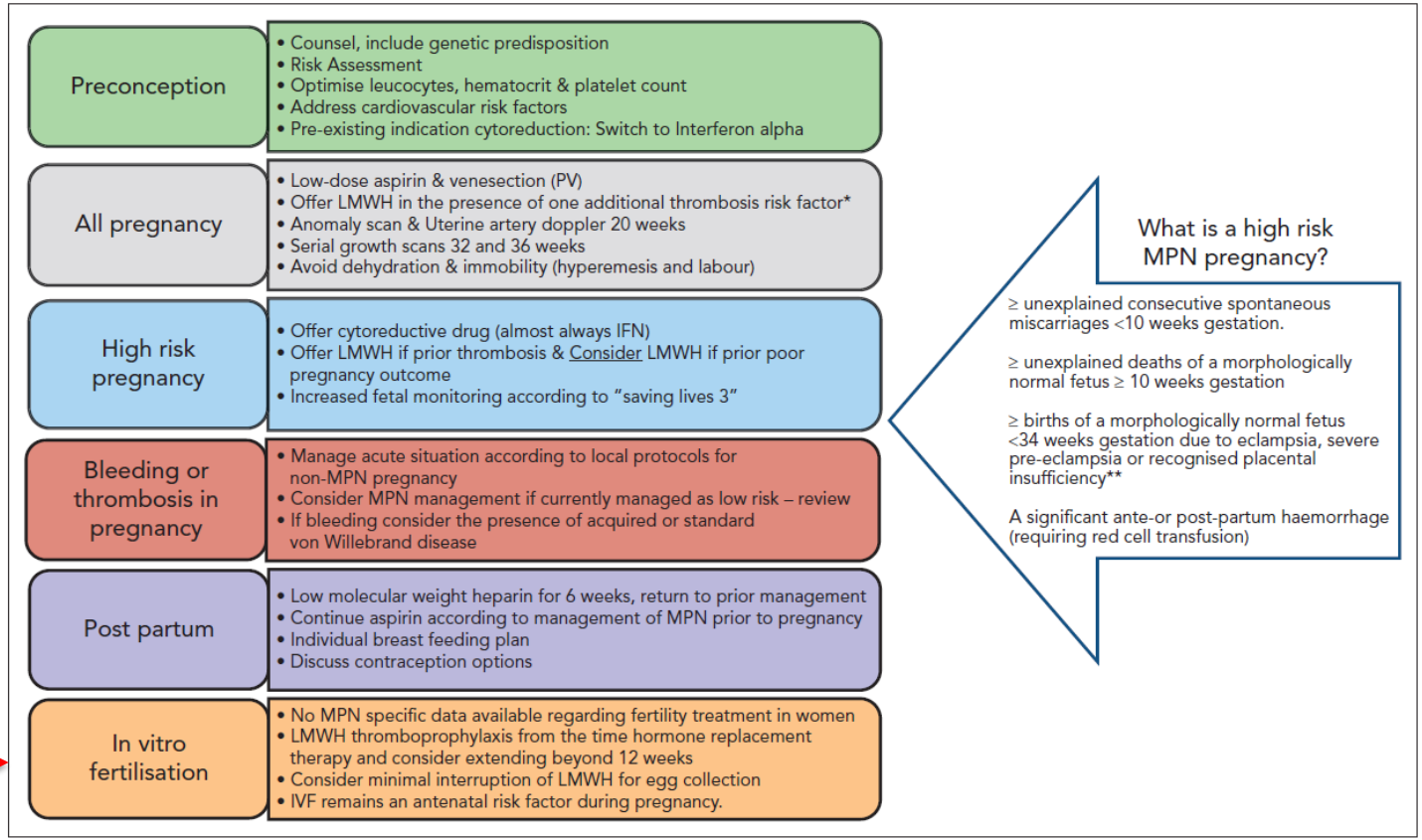

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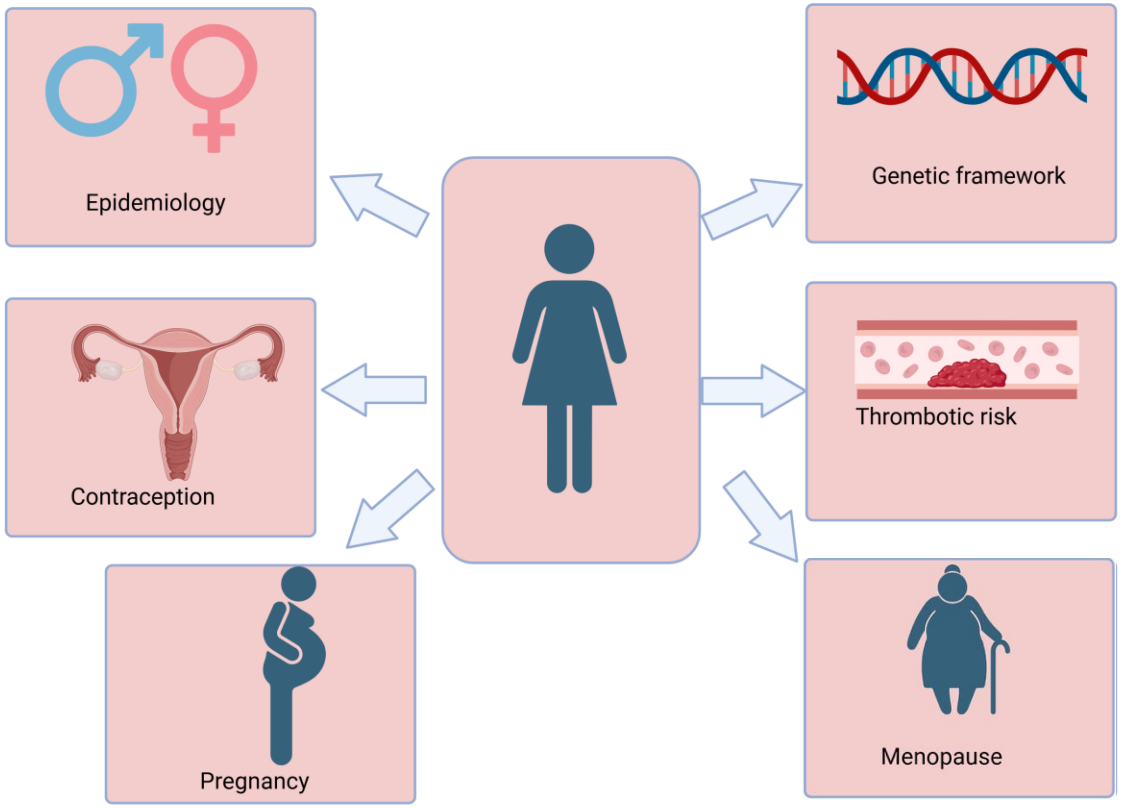
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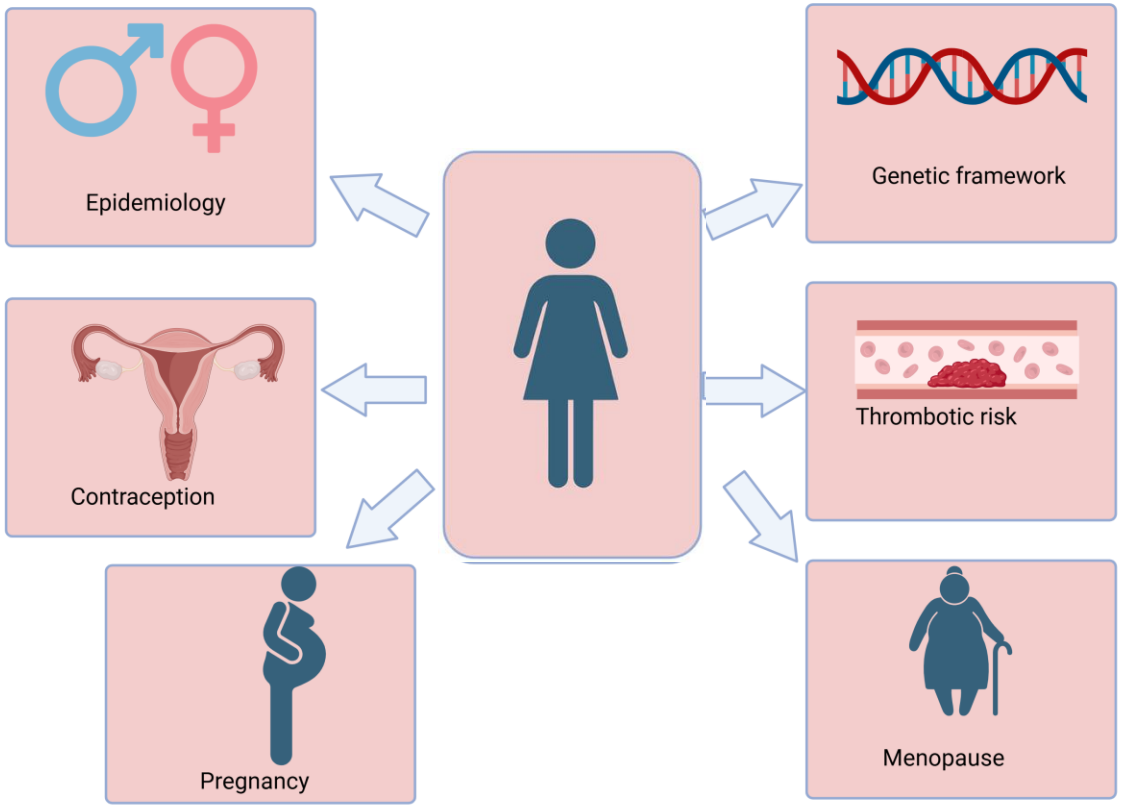
Menopause and hormone replacement (HRT)

- Estrogen-containing hormone replacement therapy should be used cautiously and only at the lowest dose possible to minimize thrombotic risk
- Women with prior thrombosis should avoid estrogen-containing HRT
- Non-estrogen or progesterone-only options are preferred if HRT is necessary
- Alternatives such as anti-depressants should be explored

Gangat N, et al. Am J Hematol. 2025; 100(Suppl 4):74-87



Thank you for your attention!

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