BOLOGNA
17 FEBBRAIO 2023
NH De La Gare

POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

Caso clinico

Paziente che desideri una gravidanza

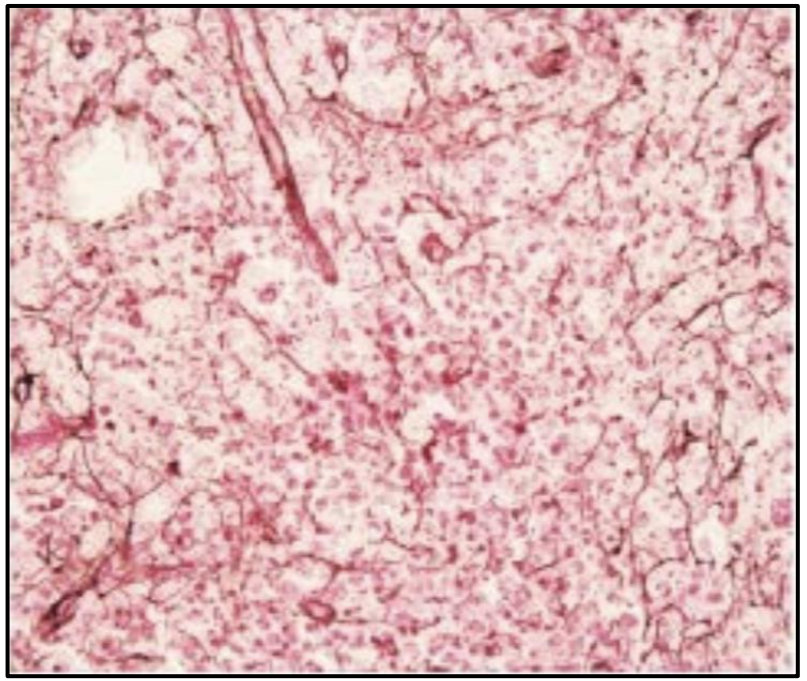
Camilla Mazzoni Istituto di Ematologia «L. e A. Seràgnoli», Università degli Studi di Bologna, IRCCS S. Orsola-Malpighi

No Disclosures

Clinical case- low-risk PV female patient

August 2009

- A 30-year-old female
- No previous thrombosis / comorbidities
- $JAK2^{V617F}$ + (55%)
- BM: fibrosis grade 1
- Normal karyotype
- Pruritus 2/10 and headache
- Overweight (BMI 27.1)
- Physical Exam unremarkable
- CBC:
  - HCT: 52.1%
  - Hb: 17.1 g/dl
  - WBC: 16 $x10^9$/l
  - Platelets: 836 $x10^9$/l



Low thrombotic risk
(age<60 yrs & no previous thrombosis)

MPN-TSS score 6 (fatigue and pruritus)

Clinical case

August 2009

- A 30-year-old female
- Low-risk PV
- BMI 26.1
- $JAK2^{V617F}$ + (55%)
- BM: fibrosis grade 1
- Normal karyotype

- Pruritus 5/10
- Headache

- Physical Exam unremarkable
- CBC:
  - HCT: 52.1%
  - Hb: 17.1 g/dl
  - WBC: 16 $x10^9$/l
  - Platelets: 836 $x10^9$/l

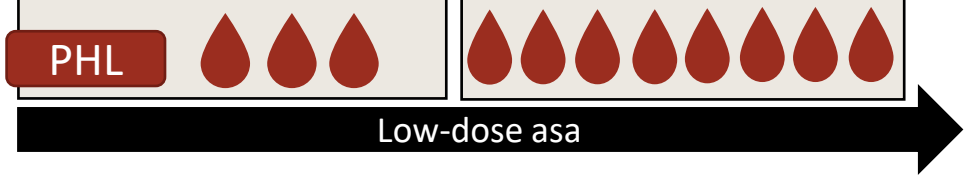
August 2012

- A 33-year-old female
- Low-risk PV
- BMI 22.5

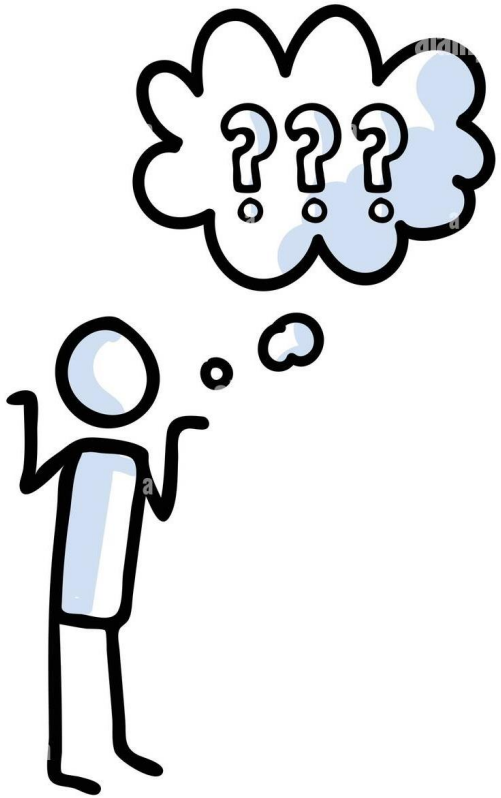
- 8 phlebotomies/yr

- Pruritus 5/10
- No headache

- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 15.7 g/dl
  - WBC: 21 x109/l
  - Platelets: 1.500 x109/l



Clinical case



What to do next?

1. Nothing, just keep it up
2. Add HU
3. Start Peg-rIFN-a
4. Start RUX
5. Repeat BMB

Prevention of vascular complications in PV

High-risk PV

Cytoreduction is mandatory if

- Age > 60 yrs
- Previous thrombosis

Low-risk PV

Cytoreduction is recommended if

- Poor PHL intolerance
- Symptomatic/progressive splenomegaly (increase by >5 cm in the past year)
- Persistent leukocytosis (WBC >20 × 10^9/L for 3 months)

Cytoreduction should be considered if

- Progressive leukocytosis (increase >100% if WBC<10x10^9/l; >50% if WBC>10x10^9/l)
- Persistent leukocytosis (>15x10^9/l for 3 months)
- PLT>1500x10^9/l for >3 mos
- ≥ 6 PHL to keep HCT<45%

Cytoreduction can be considered if

- TSS ≥20 and/or Itching ≥5 for >6 mos despite PHL, asa and antihistamines
- Relevant uncontrolled CVRF

McMullin MF, Br J Haematol. 2019 Jan;184(2):176-191. Spivak JL, Blood. 2019 Jul 25;134(4):341-352; Barbui T, Leukemia. 2018 May;32(5):1057-1069; Vannucchi AM, Haematologica. 2017 Jan;102(1):18-29. Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311.

Prevention of vascular complications in PV

High-risk PV

Cytoreduction is mandatory if

- Age > 60 yrs
- Previous thrombosis

Low-risk PV

Cytoreduction is recommended if

- Poor PHL intolerance
- Symptomatic/progressive splenomegaly (increase by >5 cm in the past year)
- Persistent leukocytosis (WBC >20 × 10^9/L for 3 months)

Cytoreduction should be considered if

- Progressive leukocytosis (increase >100% if WBC<10x10^9/l; >50% if WBC>10x10^9/l)
- Persistent leukocytosis (>15x10^9/l for 3 months)
- PLT>1500x10^9/l for >3 mos
- ≥ 6 PHL to keep HCT<45%

Cytoreduction can be considered if

- TSS ≥20 and/or Itching ≥5 for >6 mos despite PHL, asa and antihistamines
- Relevant uncontrolled CVRF

McMullin MF, Br J Haematol. 2019 Jan;184(2):176-191. Spivak JL, Blood. 2019 Jul 25;134(4):341-352; Barbui T, Leukemia. 2018 May;32(5):1057-1069; Vannucchi AM, Haematologica. 2017 Jan;102(1):18-29. Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311.

Key International PV Treatment Guidelines

ELN[1]	ESMO[2]	BCSH[3]
▪ Phlebotomy and low dose aspirin (all pts) ▪ **HU or IFN for high-risk pts**	▪ Phlebotomy and low dose aspirin (all pts) ▪ **HU or IFN for high-risk pts**	▪ Phlebotomy and low dose aspirin (all patients) ▪ **HU or IFN for high-risk pts**
▪ Ruxolitinib or interferon-α in patients who are intolerant or resistant/refractory to HU ▪ Intermittent busulphan can be considered in very elderly	▪ Ruxolitinib may be considered as second line therapy for pts who are resistant/refractory to HU ▪ Busulphan in select pts when other options contraindicated ▪ Consider clinical trials	▪ Ruxolitinib or interferon-α in patients who are intolerant or resistant/refractory to HU ▪ Busulfan or ^{32}P or pipobroman

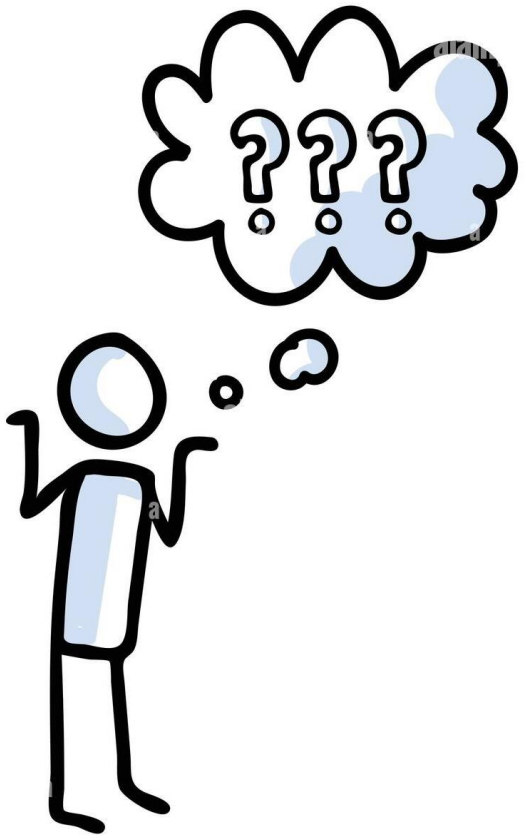
IFN unavailable in Italy at that time

HU only option

International treatment guidelines do not provide guidance on how to select hydroxyurea or interferons in first-line therapy of PV

Barbui. Leukemia. 2018;32:1057. 2. Vannucchi. Ann Oncol. 2015;26:v85. 3. McMullin. Br J Haematol. 2019;184:176.

Clinical case



What to do next?

1. Nothing, just keep it up
2. **Add HU**
3. Start Peg-rIFN-a
4. Start RUX
5. Repeat BMB

Clinical case

HU 500 mg/d

August 2009

- A 30-year-old female
- Low-risk PV
- BMI 26.1
- $JAK2^{V617F}$ + (55%)
- BM: fibrosis grade 1
- Normal karyotype
- Pruritus 5/10
- Headache
- Physical Exam unremarkable
- CBC:
  - HCT: 52.1%
  - Hb: 17.1 g/dl
  - WBC: 16 $x10^9$/l
  - Platelets: 836 $x10^9$/l

PHL

August 2012

- A 33-year-old female
- Low-risk PV
- BMI 22.5
- 8 phlebotomies/yr
- Pruritus 5/10
- No headache
- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 15.7 g/dl
  - WBC: 21 $x10^9$/l
  - Platelets: 1.500 $x10^9$/l

August 2013

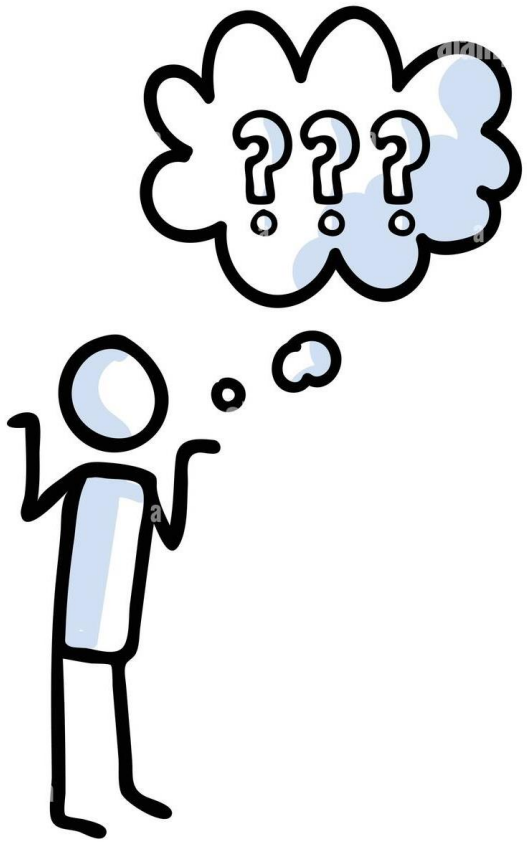
- A 34-year-old female
- Low-risk PV
- No vascular events
- 2 phlebotomies/yr
- Pruritus 6/10
- Physical Exam unremarkable
- CBC:
  - HCT: 44.1%
  - Hb: 13.1 g/dl
  - WBC: 14 $x10^9$/l
  - Platelets: 990 $x10^9$/l

GI toxicity

- **Requires therapy optimization**

Low-dose asa

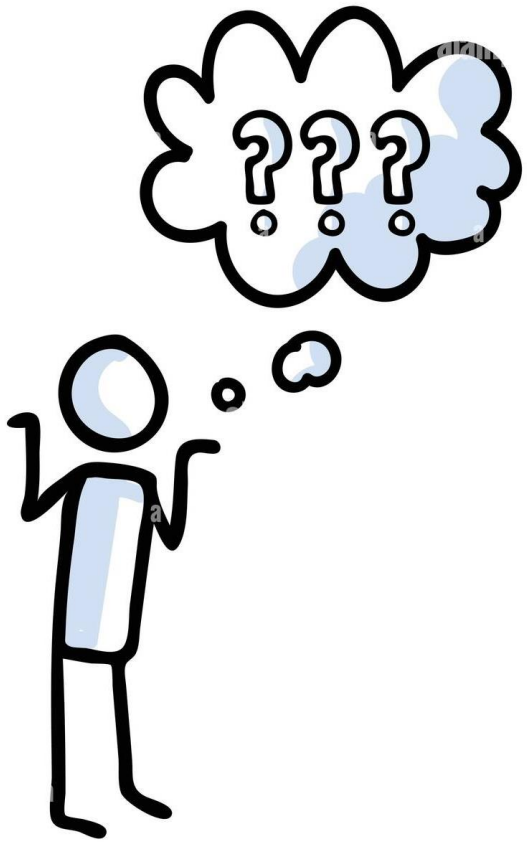
Clinical case



How to go on?

1. Nothing, just keep it up
2. Start Peg-rIFN-a
3. Start RUX
4. Repeat BMB

Clinical case

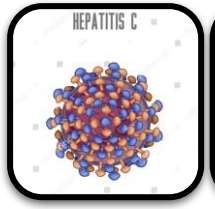


How to go on?

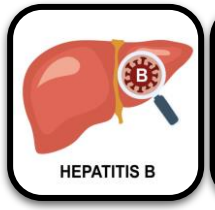
1. Nothing, just keep it up
2. Start Peg-rIFN-a
3. **Start RUX**
4. Repeat BMB

Clinical case

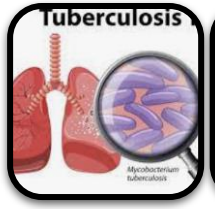
Screening for RUX start



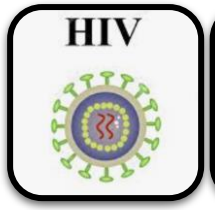
HCV IgG neg



HBV serology neg



Quantiferon neg



HIV neg

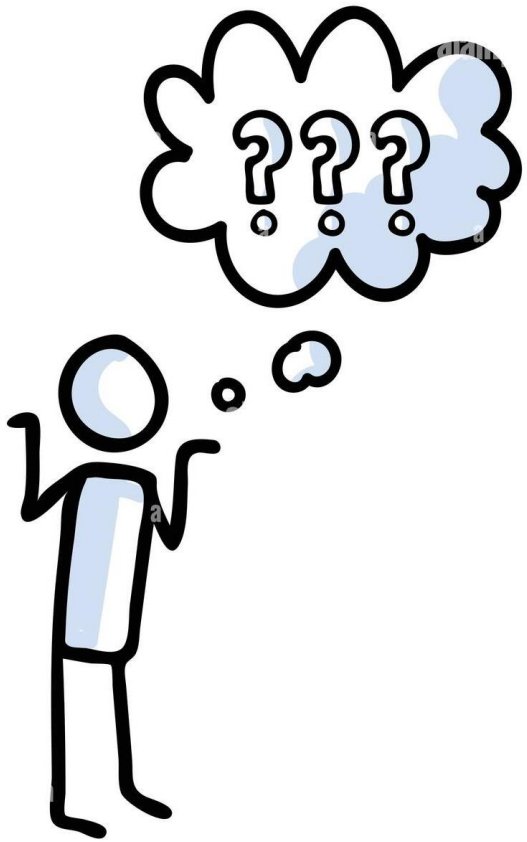
Clinical case

HU 500 mg/d → RUX 10 mg BID

August 2009	August 2012	August 2013	August 2015
▪ A 30-year-old female ▪ Low-risk PV ▪ BMI 26.1 ▪ $JAK2^{V617F}$ + (55%) ▪ BM: fibrosis grade 1 ▪ Normal karyotype	▪ A 33-year-old female ▪ Low-risk PV ▪ BMI 22.5	▪ A 34-year-old female ▪ Low-risk PV ▪ No vascular events	▪ A 36-year-old female ▪ Low-risk PV ▪ No vascular events
▪ 8 phlebotomies/yr		▪ 2 phlebotomies/yr	▪ 0 phlebotomies/yr
▪ Pruritus 5/10 ▪ Headache	▪ Pruritus 5/10 ▪ No headache	▪ Pruritus 6/10 ▪ Physical Exam unremarkable	▪ Pruritus 0/10 ▪ Physical Exam unremarkable
▪ Physical Exam unremarkable ▪ CBC: ▪ HCT: 52.1% ▪ Hb: 17.1 g/dl ▪ WBC: 16 $x10^9$/l ▪ Platelets: 836 $x10^9$/l	▪ Physical Exam unremarkable ▪ CBC: ▪ HCT: 47.1% ▪ Hb: 15.7 g/dl ▪ WBC: 21 $x10^9$/l ▪ Platelets: 1.500 $x10^9$/l	▪ CBC: ▪ HCT: 44.1% ▪ Hb: 13.1 g/dl ▪ WBC: 14 $x10^9$/l ▪ Platelets: 990 $x10^9$/l	▪ CBC: ▪ HCT: 43.1% ▪ Hb: 12.1 g/dl ▪ WBC: 9 x109/l ▪ Platelets: 358 $x10^9$/l
		▪ **GI toxicity** ▪ **Requires therapy optimization**	▪ **Motherhood desire**
PHL			

Low-dose asa

Clinical case



What about now?

1. Pregnancy is contraindicated
2. Continue RUX during pregnancy
3. Stop RUX and W&W
4. Start Peg-rIFN-a

Pregnancy in PV patients

Pregnancies in women with PV and PMF are rare, since the majority of patients are older than age 60 years at time of their diagnosis; PV has a male preponderance with only 15% of patients diagnosed before age 40 years.

As both MPN and pregnancy are associated with a higher incidence of thromboembolic and hemorrhagic complications, a dramatic increase in such complications is a matter concern, if a woman with MPN gets pregnant.

MPN promotes thrombotic and bleeding environment and is associated with an increased risk of placental thrombosis, intrauterine growth retardation or loss.

Palandri F. et al. Ann Hematol. 2021 Jan;100(1):11-25.Gangat N et al. Am J Hematol. 2021 Mar 1;96(3):354-366.

Pregnancy in PV patients

Study				Maternal outcome				Fetal outcome				
	Patient/ Pregnancy	Treatment pre-pregnancy	Treatment during pregnancy	Thrombotic events	Major bleeding	Pre-eclampsia	Placenta abruption	Patients with prior pregnancy loss	Miscarriage and elective abortion	Live birth	Preterm delivery	IUGR
	n	n,%	n,%	n,%	n,%	n,%	n,%	n,%	n,%	n,%	n,%	n,%
(Robinson et al. 2005)	8/18 (19 fetuses)	NA	INF+ ASA + LMWH 11 (61.1)	1 (5.6)	None	3 (16.7)	2 (11.1)	2 (25)	4 (22.2)	11 (61.1)	3 (16.7)	3 (16.7)
(Griessham mer et al. 2016)	48/121	NA	INF 12 (10)	3 (2)	3 (2)	NA	NA	NA	28/115 (24)	73/115 (64)	NA	NA
(Lapoirie et al. 2018)	8/5	ASA 7 (87.5) VKA 2 (25) INF 3 (37.5)	ASA 3 (37.5) ASA+ LMWH+ INF 2 (25) ASA+ LMWH 2 (25) LMWH 1 (12.5)	1 (12.5)	2 (25)	1 (12.5)	None	2 (25)	1 (12.5)	7 (87.5)	2 (25)	3 (37.5)
(Bertozzi et al. 2018)	15/25	NA	ASA 16 (40) ASA+ LMWH 3 (12) INF 1 (4) None 5 (20)	Maternal complications: 4(16.7)				NA	7/24 (29.2)	15/24 (62.5)	5/24 (20.8)	1/24 (4.2)
(Gangat et al. 2020)	4/5	NA	ASA 2 (29) ASA+ LMHW 2 (29)	1 (20)	None	None	None	1 (20)	None	5 (100)	None	NA

Pregnancy recommendations

Pregnancy pre-conception meeting and evaluation by high-risk obstetrician is recommended.

All females with PV should maintain hematocrit, ideally, below the gestational range (<41% trimester 1, <38% trimester 2, <39% trimester 3).

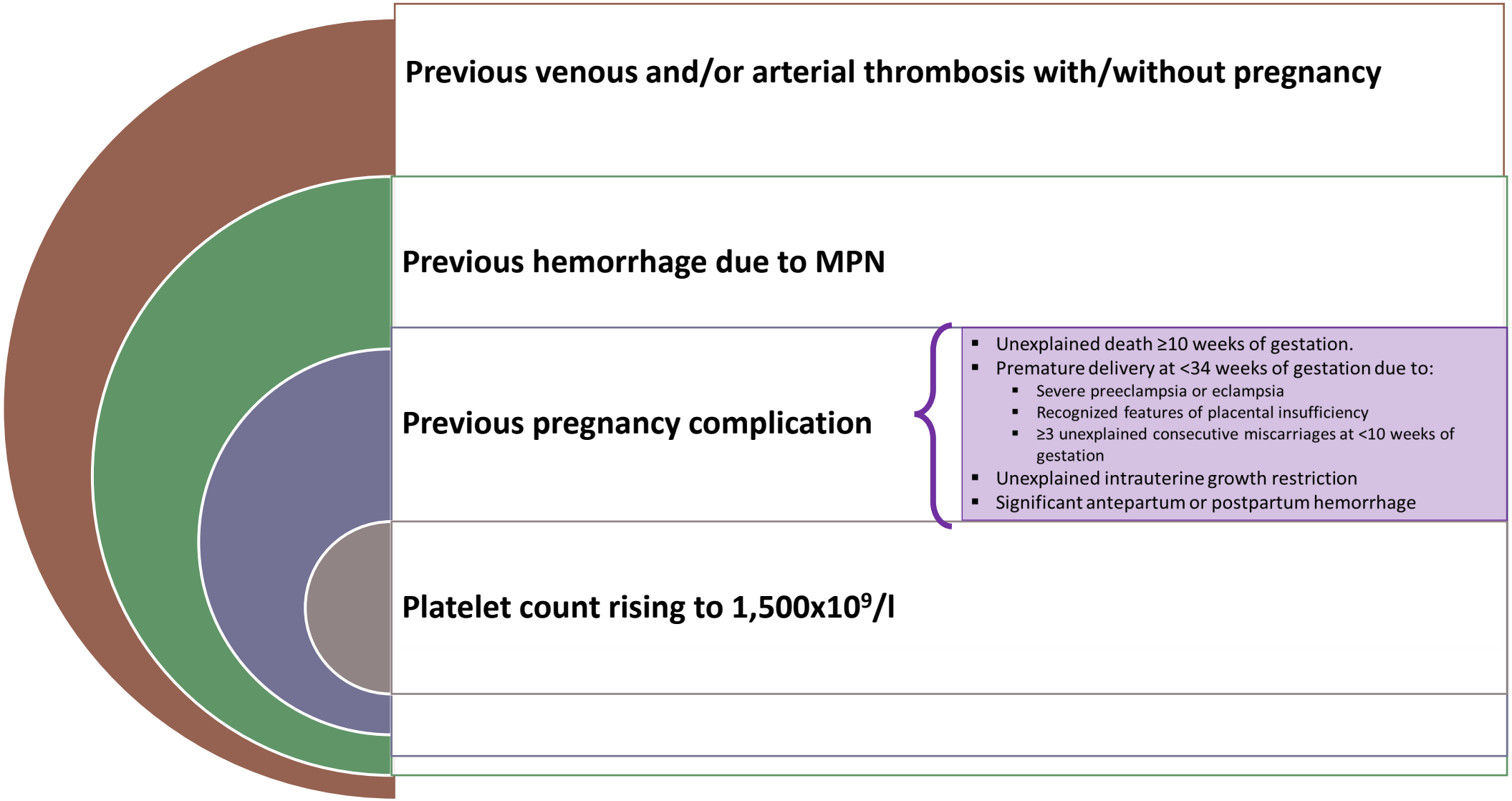
Hydroxyurea and/or ruxolitinib should be discontinued in anticipation of pregnancy or, if pregnancy unplanned, as soon as the pregnancy is established.

If cytoreductive therapy is needed during pregnancy, interferons can be considered. Potential indications include those with prior pregnancy loss or complications (pre-eclampsia), or uncontrolled leukocytosis/thrombocytosis.

While IFN are classified as risk category C during pregnancy, they can be used if benefits outweigh potential risk to the fetus.

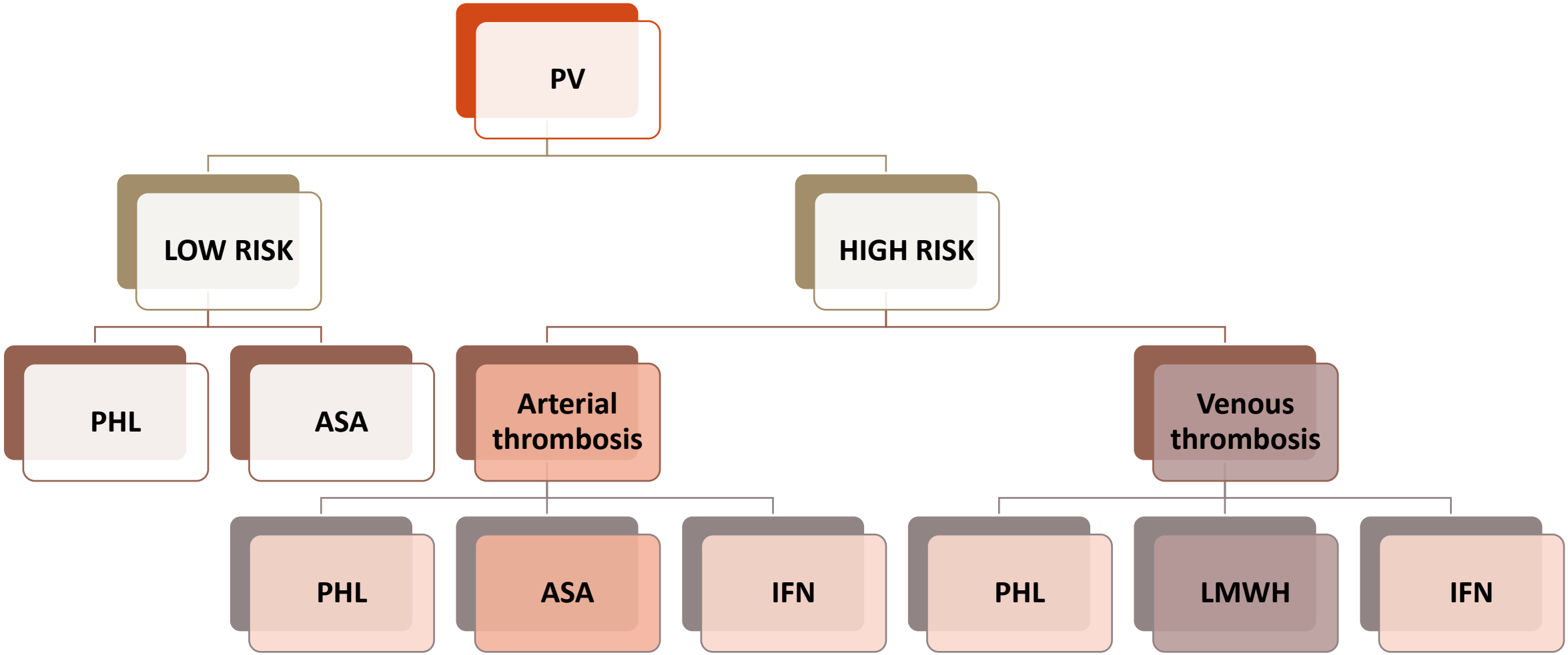
Beauverd Y et al. Haematologica 2016 ;101:e182-e184. Lishner M, et al. J Clin Oncol 7 2016;34:501-508 .Maze D, et al. 2018;132(Suppl 1):3046-3046.

Definition of High-Risk PV Pregnancy



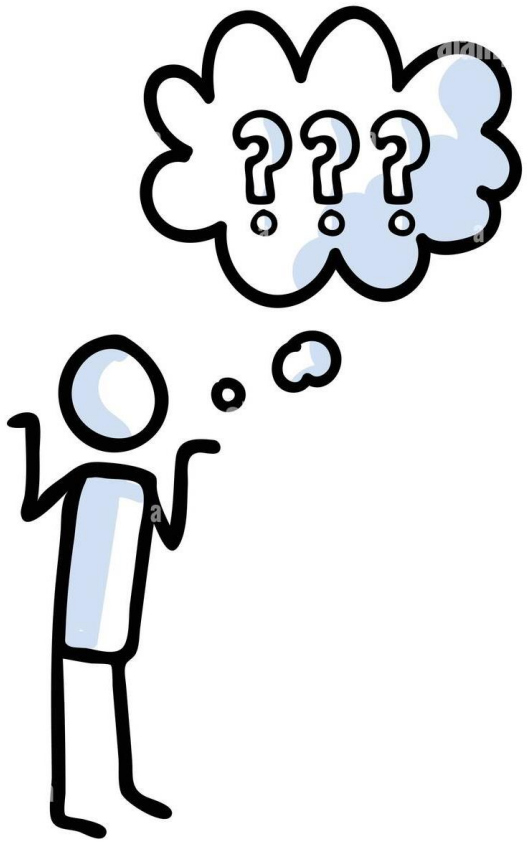
Griesshammer M. et al. Expert Rev Hematol 2018 Sep;11(9):697-706.

Management of Pregnancy in PV



Gangat N et al. Am J Hematol. 2021 Mar 1;96(3):354-366.

Clinical case



What about now?

1. Pregnancy is contraindicated
2. Continue RUX during pregnancy
3. **Stop RUX and W&W**
4. Start Peg-rIFN-a

Clinical case

HU 500 mg/d → RUX 10 mg BID

August 2009	August 2012	August 2013	August 2015
▪ A 30-year-old female ▪ Low-risk PV ▪ BMI 26.1 ▪ JAK2^{V617F} + (75%) ▪ BM: fibrosis grade 1 ▪ Normal karyotype	▪ A 33-year-old female ▪ Low-risk PV ▪ BMI 22.5	▪ A 34-year-old female ▪ Low-risk PV ▪ No vascular events	▪ A 36-year-old female ▪ Low-risk PV ▪ No vascular events
▪ 8 phlebotomies/yr		▪ 2 phlebotomies/yr	▪ 0 phlebotomies/yr
▪ Pruritus 5/10 ▪ Headache	▪ Pruritus 5/10 ▪ No headache	▪ Pruritus 6/10 ▪ Physical Exam unremarkable	▪ Pruritus 0/10 ▪ Physical Exam unremarkable

▪ Physical Exam unremarkable
▪ CBC:
  ▪ HCT: 52.1%
  ▪ Hb: 17.1 g/dl
  ▪ WBC: 16 x10^9/l
  ▪ Platelets: 836 x10^9/l
	▪ Physical Exam unremarkable
	▪ CBC:
	  ▪ HCT: 47.1%
	  ▪ Hb: 15.7 g/dl
	  ▪ WBC: 21 x10^9/l
	  ▪ Platelets: 1.500 x10^9/l
		▪ CBC:
		  ▪ HCT: 44.1%
		  ▪ Hb: 13.1 g/dl
		  ▪ WBC: 14 x10^9/l
		  ▪ Platelets: 990 x10^9/l
			▪ CBC:
			  ▪ HCT: 43.1%
			  ▪ Hb: 12.1 g/dl
			  ▪ WBC: 9 x109/l
			  ▪ Platelets: 358 x10^9/l

PHL		▪ **GI toxicity** ▪ **Requires therapy optimization**	▪ **Motherhood desire**

Low-dose asa

February 2, 2017

Clinical case

HU 500 mg/d → RUX 10 mg BID

August 2009

- A 30-year-old female
- Low-risk PV
- BMI 26.1
- JAK2^{V617F} + (75%)
- BM: fibrosis grade 1
- Normal karyotype
- Pruritus 5/10
- Headache
- Physical Exam unremarkable
- CBC:
  - HCT: 52.1%
  - Hb: 17.1 g/dl
  - WBC: 16 x10^9/l
  - Platelets: 836 x10^9/l

PHL

August 2012

- A 33-year-old female
- Low-risk PV
- BMI 22.5
- 8 phlebotomies/yr
- Pruritus 5/10
- No headache
- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 15.7 g/dl
  - WBC: 21 x10^9/l
  - Platelets: 1.500 x10^9/l

August 2013

- A 34-year-old female
- Low-risk PV
- No vascular events
- 2 phlebotomies/yr
- Pruritus 6/10
- Physical Exam unremarkable
- CBC:
  - HCT: 44.1%
  - Hb: 13.1 g/dl
  - WBC: 14 x10^9/l
  - Platelets: 990 x10^9/l
- **GI toxicity**
- **Requires therapy optimization**

August 2015

- A 36-year-old female
- Low-risk PV
- No vascular events
- 0 phlebotomies/yr
- Pruritus 0/10
- Physical Exam unremarkable
- CBC:
  - HCT: 43.1%
  - Hb: 12.1 g/dl
  - WBC: 9 x109/l
  - Platelets: 358 x10^9/l
- **Motherhood desire**

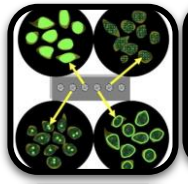
August 2020

- A 41-year-old female
- Low-risk PV
- JAK2^{V617F} + (75%)
- BM: fibrosis grade 1
- Normal karyotype
- **6 phlebotomies/yr**
- Pruritus 5/10
- Physical Exam unremarkable
- CBC:
  - **HCT: 47.1%**
  - Hb: 16.1 g/dl
  - WBC: 21 x10^9/l
  - **Platelets: 879 x10^9/l**
- **Need for cytoreduction**

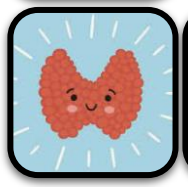
Low-dose asa

Clinical case

Screening for IFN start



ANA reflex neg



Anti tyreo-globulin and anti tyreo-peroxidase antibodies neg

Rheumatoid factor and anti phospholipid antibodies within normal limits

No history of diabetes nor other autoimmune disease

No history of psychiatric disorders

Clinical case

HU 500 mg/d → RUX 10 mg BID → ropegIFNa2b 100 mcg/2 weeks

August 2009

- A 30-year-old female
- Low-risk PV
- BMI 26.1
- JAK2^{V617F} + (55%)
- BM: fibrosis grade 1
- Normal karyotype
- Pruritus 5/10
- Headache
- Physical Exam unremarkable
- CBC:
  - HCT: 52.1%
  - Hb: 17.1 g/dl
  - WBC: 16 x10^9/l
  - Platelets: 836 x10^9/l

PHL

August 2012

- A 33-year-old female
- Low-risk PV
- BMI 22.5
- 8 phlebotomies/yr
- Pruritus 5/10
- No headache
- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 15.7 g/dl
  - WBC: 21 x10^9/l
  - Platelets: 1.500 x10^9/l

August 2013

- A 34-year-old female
- Low-risk PV
- No vascular events
- 2 phlebotomies/yr
- Pruritus 6/10
- Physical Exam unremarkable
- CBC:
  - HCT: 44.1%
  - Hb: 13.1 g/dl
  - WBC: 14 x109/l
  - Platelets: 990 x10^9/l
- **GI toxicity**
- **Requires therapy optimization**

August 2015

- A 36-year-old female
- Low-risk PV
- No vascular events
- 0 phlebotomies/yr
- Pruritus 0/10
- Physical Exam unremarkable
- CBC:
  - HCT: 43.1%
  - Hb: 12.1 g/dl
  - WBC: 9 x10^9/l
  - Platelets: 358 x10^9/l
- **Motherhood desire**

August 2020

- A 41-year-old female
- Low-risk PV
- JAK2^{V617F} + (75%)
- BM: fibrosis grade 1
- Normal karyotype
- 6 phlebotomies/yr
- Pruritus 5/10
- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 16.1 g/dl
  - WBC: 21 x10^9/l
  - Platelets: 879 x10^9/l
- **Need for cytoreduction**

Low-dose asa

Clinical case

HU 500 mg/d → RUX 10 mg BID → ropegIFNa2b 100 mcg/2 weeks

August 2009

- A 30-year-old female
- Low-risk PV
- BMI 26.1
- $JAK2^{V617F}$ + (55%)
- BM: fibrosis grade 1
- Normal karyotype
- Pruritus 5/10
- Headache
- Physical Exam unremarkable
- CBC:
  - HCT: 52.1%
  - Hb: 17.1 g/dl
  - WBC: 16 $x10^9$/l
  - Platelets: 836 $x10^9$/l

PHL

August 2012

- A 33-year-old female
- Low-risk PV
- BMI 22.5
- 8 phlebotomies/yr
- Pruritus 5/10
- No headache
- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 15.7 g/dl
  - WBC: 21 $x10^9$/l
  - Platelets: 1.500 $x10^9$/l

August 2013

- A 34-year-old female
- Low-risk PV
- No vascular events
- 2 phlebotomies/yr
- Pruritus 6/10
- Physical Exam unremarkable
- CBC:
  - HCT: 44.1%
  - Hb: 13.1 g/dl
  - WBC: 14 $x10^9$/l
  - Platelets: 990 $x10^9$/l
- **GI toxicity**
- **Requires therapy optimization**

August 2015

- A 36-year-old female
- Low-risk PV
- No vascular events
- 0 phlebotomies/yr
- Pruritus 0/10
- Physical Exam unremarkable
- CBC:
  - HCT: 43.1%
  - Hb: 12.1 g/dl
  - WBC: 9 $x10^9$/l
  - Platelets: 358 $x10^9$/l
- **Motherhood desire**

August 2020

- A 41-year-old female
- Low-risk PV
- $JAK2^{V617F}$ + (75%)
- BM: fibrosis grade 1
- Normal karyotype
- 6 phlebotomies/yr
- Pruritus 5/10
- Physical Exam unremarkable
- CBC:
  - HCT: 47.1%
  - Hb: 16.1 g/dl
  - WBC: 21 $x10^9$/l
  - Platelets: 879 $x10^9$/l
- **Need for cytoreduction**

August 2022

- A 42-year-old female
- Low-risk PV
- $JAK2^{V617F}$ + (19%)
- BM: not available
- 0 phlebotomies/yr
- Pruritus 0/10
- Physical Exam unremarkable
- CBC:
  - HCT: 42.1%
  - Hb: 12.5 g/dl
  - WBC: 8.9 $x10^9$/l
  - Platelets: 389 $x10^9$/l

Low-dose asa

Conclusions

- In PV maternal morbidity and stillbirth are significantly increased compared with the situation in ET.
- Pregnancy in PV necessarily requires an active management with control of hematocrit, aspirin, post-partum prophylactic low molecular weight heparin (LMWH) and in some higher risk cases interferon alpha and/or LMWH throughout pregnancy.
- After delivery, prophylactic LMWH should be given for six weeks post-partum because this is the most dangerous period for maternal thromboembolic events.
- In high risk MPN requiring cytoreductive therapy during pregnancy interferon alpha is the drug of choice. Pegylated interferon alpha should be preferred due to better tolerability and efficacy, although safety issues cannot completely be ruled out.

BOLOGNA
17 FEBBRAIO 2023
NH De La Gare

POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

GRAZIE!