

**TERZO  
MEETING  
DI EMATOLOGIA  
NON  
ONCOLOGICA**

**Boscolo Hotel Astoria  
Firenze 26-27 gennaio 2017**

***Gravidanza e MPN***

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# Outlines

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- Risk of obstetric complications in MPN
- Risk of pregnancy-related thrombosis in MPN
- Treatment of pregnant MPN women

Table 1 Essential thrombocythemia and pregnancy – Obstetrical outcome in 291 pregnancies reported in the literature (Reports on > 10 Pregnancies or > 5 patient)

Reference	Patients	Pregnancies	Live births	Miscarriages
Belluci et al. 1986	3	11	4	7
Beard et al. 1991	6	9	8	1
Leone et al. 1991	8	10	7	3
Beressi et al. 1995	18	34	17	17
Pagliari et al. 1996	9	15	9	6
Randi et al. 1999	13	16	13	3
Bangerter et al. 2000	9	17	11	6
Wright et al. 2001	20	43	22	21
Niittyvuopio et al. 2004	16	40	25	15
Passamonti et al. 2007	58	96	62	34
<b>Total</b>	<b>160</b>	<b>291</b>	<b>178 (61%)</b>	<b>113 (39%)</b>

*Griesshammer et al, Blood Rev 2008*

**Table 2 Essential Thrombocythemia and Pregnancy: Obstetric complications in 275 pregnancies reported in the literature (reports on >10 Pregnancies or >5 patients)**

Reference	Pregnancies	FTND	SA	SB	PTD	Remarks
Belluci et al. 1986 <sup>15</sup>	11	2	6	—	2	1 AP
Beard et al. 1991 <sup>5</sup>	9	7	1	—	1	—
Leone et al. 1991 <sup>16</sup>	10	7	—	3	—	—
Beressi et al. 1995 <sup>6</sup>	34	15	12	1	2	1 AP, 1 EP, 2 EA
Pagliaro et al. 1996 <sup>17</sup>	15	6	2	3	3	1 EA
Bangerter et al. 2000 <sup>4</sup>	17	7	6	—	3	IPoTND
Wright et al. 2001 <sup>19</sup>	43	21	16	1	1	1 AP, 1 EP, 2 EA
Niittyvuoplo et al. 2004 <sup>10</sup>	40	23	13	2	2	3 ECL
Passamonti et al. 2007	96	58	31	3	4	4 pre-ECL
<b>Total</b>	<b>275</b>	<b>146 (53%)</b>	<b>87 (32%)</b>	<b>13 (5%)</b>	<b>18 (7%)</b>	

FTND: full-term normal delivery (including forceps and caesarian section), SA: spontaneous abortion, SB: stillbirth, PTD: pre-term delivery, PoTND: post term normal delivery; EA: elective abortion; EP: ectopic pregnancy; AP: abruptio placentae, ECL: eclampsia.

*Griesshammer et al, Blood Rev 2008*

**Table 3** Essential thrombocythemia and pregnancy – Maternal complications in 291 pregnancies reported in the literature (Reports on >10 Pregnancies or >5 patients)

Reference	Pregnancies	Major Thrombosis	Major Bleeding	Remarks
Belluci et al. 1986	11	—	—	—
Beard et al. 1991	9	1	1	1 leg ulcer, 1 hemorrhage following spontaneous abortion
Leone et al. 1991	10	3	—	1 ileofemoral and 2 mesenteric thromboses
Beressi et al. 1995	34	—	—	—
Pagliari et al. 1996	15	1	1	1 Budd Chiari, 1 severe bleeding after abortion
Randi et al. 1999	16	1	—	1 sagittal sinus thrombosis 3 days after delivery
Bangerter et al. 2000	17	1	3	1 transient visual loss, 2 vaginal bleedings, 1 bleeding after caesarian section
Wright et al. 2001	43	—	—	—
Niittyvuopio et al. 2004	40	—	1	2 pre-eclampsia, 1 eclampsia, 2 microcirculatory disturbances, 1 hemorrhage during caesarian section
Passamonti et al. 2007	96	1	0	5 pre-eclampsia, 4 arterial hypertension
<b>Total</b>	<b>291</b>	<b>8 (3%)</b>	<b>6 (2%)</b>	

*Griesshammer et al, Blood Rev 2008*

# Pregnancies in MPN (ELN – WP 9)

## - update 02/2015 -

### 9 countries

- Austria
- Czech Republic
- Denmark
- France
- Germany
- Italy
- Romania
- Slovakia
- Switzerland

317 pregnancies in 154 patients

- Essential thrombocythemia
  - n = 115 (239 pregnancies)
- Polycythemia vera
  - n = 30 (69 pregnancies)
- Primary myelofibrosis
  - n = 9

## **Pregnancies in MPN (ELN – WP 9)**

### **- preliminary results: Conclusions -**

#### **Pregnancy outcome in 285 of 317 pregnancies<sup>1) 2) 3)</sup>**

- Live birth rate 75% (ET: 78%, PV 72%)
- Spontaneous abortions ~ 21% (ET: 20%, PV 27%)
- Major bleeding ~ 3,5 % (ET: 3%, PV:7%)
- Venous Thrombosis VTE ~ 1% (ET: 1%, PV: 2%)

1) elective abortions: n=13    2) pregnancies ongoing: n=19    3) pregnancy before diagnosis MPN: n=68

# Pregnancy complications predict thrombotic events in young women with essential thrombocythemia

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Although Philadelphia-negative myeloproliferative neoplasms (MPNs) occur typically in middle to advanced age, any age group may be affected, posing a challenge for their management during pregnancy when they occur in young females. There is a high incidence of thromboembolic events and pregnancy complications in patients with myeloproliferative neoplasms, and a possible relationship between these complications is a matter of concern. The aim of this article was to correlate thrombosis and pregnancy outcome in 158 females with ET experiencing 237 pregnancies. Seven patients had a thrombotic event before their first pregnancy, one of them ended (14.3%) in a miscarriage. Among the 151 patients with no history of thrombosis before they became pregnant, 40 (26.5%) had a miscarriage ( $P = \text{NS}$ ). Eighteen patients (11.4%) developed major thrombotic complications (12 splanchnic vein, 1 cerebral vein, 2 coronary syndromes, and 3 strokes) after at least one pregnancy (4 uneventful and 14 complicated). The occurrence of thrombosis was significantly more frequent ( $P < 0.001$ ) in patients with a history of pregnancy complications (28%) than in those experiencing a normal pregnancy and delivery (3.7%). Pregnancy complications in women with ET are associated with a higher risk of subsequent thromboses, so pregnant women with this neoplasm who miscarry need to be carefully monitored.

Am. J. Hematol. 89:306–309, 2014. © 2013 Wiley Periodicals, Inc.



**TABLE I.** Demographic, Hematological Characteristics, and Pregnancies Outcomes and Complications of 158 Pregnant Women With ET

No. of patients	158
Median age years (range)	28 (17–40)
Median leukocyte count $\times 10^9/L$ (range)	10.9 (3.24–27.1)
No. of pats with WBC $> 10 \times 10^9/L$	46 (29%)
Median hemoglobin $g/dL^{-1}$ (range)	14 (8.5–15)
Median platelet count $\times 10^9/L$ (range)	1093 (500–3140)
No. of patients with platelets $> 1,500 \times 10^9/L$	17 (10.7%)
No. of patients with at least 1 abortion risk factor <sup>a</sup>	29 (18%)
No. of patients with thrombophilia and/or cardiovascular risk factors <sup>b</sup>	10 (6.3%)
Pregnancies	237
Uneventful	152
Total pregnancies events	85 (36%)
Fetal loss	69 (29%)
First trimester abortion	60 (87%)
Second/third trimester abortion	8 (11.5%)
Stillbirth	1 (1.5%)
Maternal complications	16 (7%)
Pre-eclampsia (resolved after delivery)	9 (56%)
Arterial hypertension (resolved after delivery)	7 (44%)

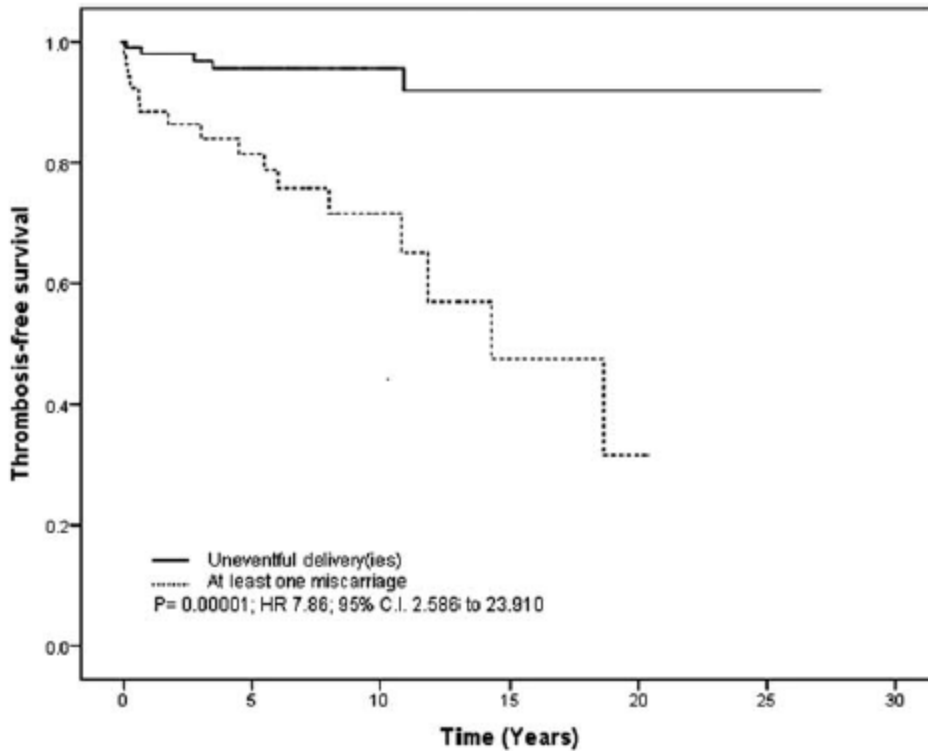
<sup>a</sup> Age, smoking, diabetes, hypertension, hyperlipidemia, thrombophilia.

<sup>b</sup> Smoking, diabetes, hypertension, hyperlipidemia, oral contraception, lupus anticoagulant, congenital thrombophilia.

*Randi et al, Am J Hematol 2014*

**TABLE III.** Multivariate Analysis for Risk Factors Predicting Thrombotic Events After Pregnancy in ET Females

Parameters at diagnosis	Thrombosis (n = 18)	
	HR (95% CI)	P
WBC > 10 × 10 <sup>9</sup> /L	1.12 (0.84–1.5)	0.434
Platelets > 1,000 × 10 <sup>9</sup> /L	0.99 (0.99–1)	0.074
JAK2 V617F/WT	0.64 (0.15–2.46)	0.554
Hemoglobin < 120 g/dL <sup>-1</sup>	0.92 (0.31–2.7)	0.890
Hematocrit > 45%	1.0 (6.9–1.45)	0.976
Previous miscarriage yes/no	9.33 (2.35–36.97)	0.001
Age at diagnosis	1.0 (0.94–1.2)	0.301
CV risk factors <sup>a</sup>	6.57 (1.42–30.25)	0.016



*Randi et al, Am J Hematol 2014*

# Risk stratification and treatment

If all of the following factors are present then the pregnancy should be considered at low risk:

1. No prior ET related complications, and
2. Absence of hereditary thrombophilic factors, and
3. Age <35 years
4. Platelet count  $<1000 \times 10^9/l$

*Griesshammer et al, Blood Reviews 2008*

If any of the following factors are present then the pregnancy should be considered at high risk:

1. Previous microcirculatory disturbances, or
2. Presence of two or more hereditary thrombophilic factors (e.g. Factor V Leiden mutation plus a positive lupus anticoagulants etc.), or
3. Severe complications in a previous pregnancy ( $\geq 3$  first trimester losses or  $\geq 1$  second or third trimester pregnancy loss, birth weight <5th centile for gestation, intrauterine death or stillbirth, stillbirth and pre-eclampsia necessitating preterm delivery <37 weeks, or development of any such complication in the index pregnancy, or
4. Platelet count  $>1000 \times 10^9/l$ , or
5. Age >35 years

If any of the following factors are present then the pregnancy should be considered at highest risk:

1. Actual thrombosis, or thromboembolic event during the last six months, or
2. Previous maternal major thromboembolic or major hemorrhagic complications.

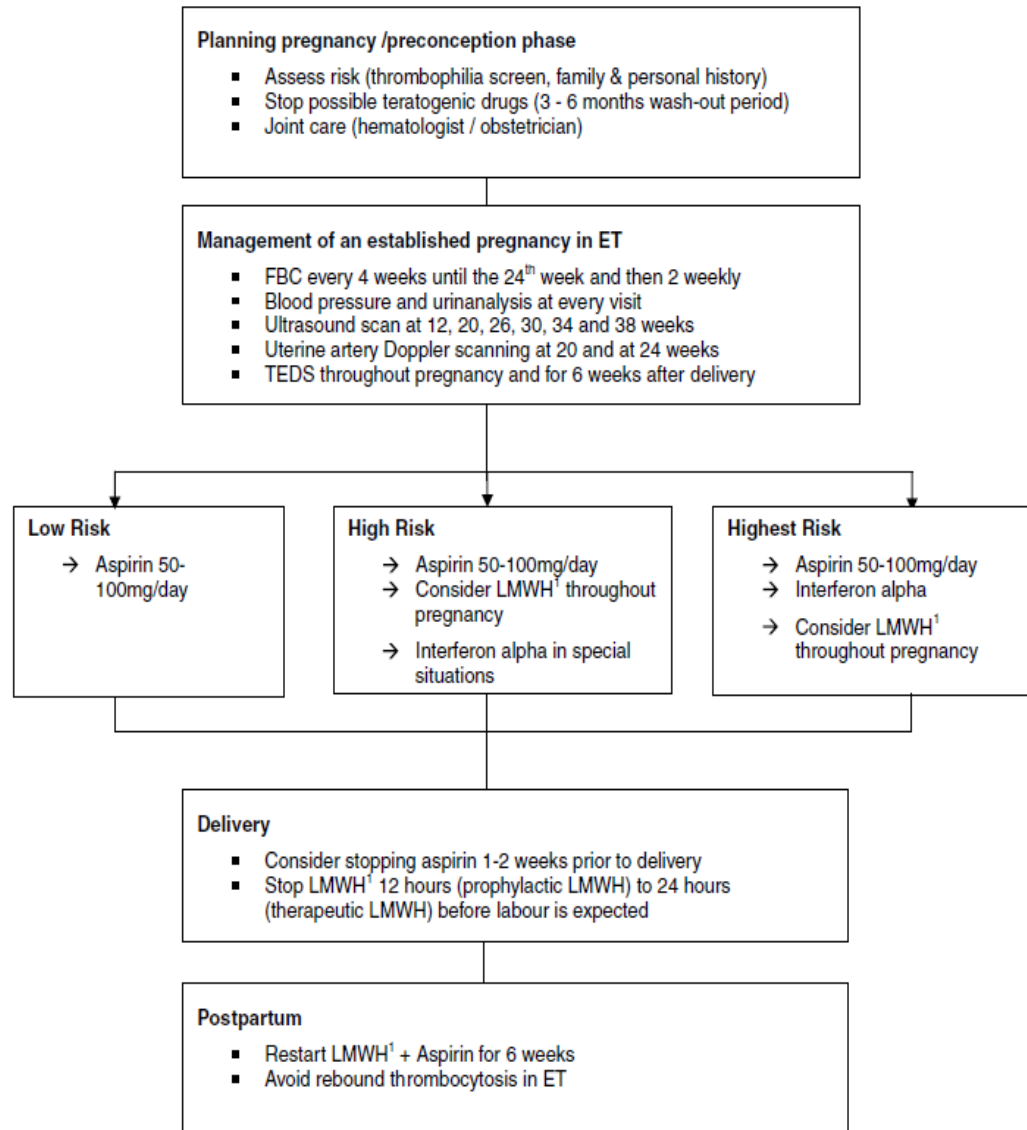


Figure 1 Suggested management algorithm of pregnancy in ET. <sup>1</sup>Enoxaparin 40 mg or dalteparin 5000 IU. FBC: full blood count; TEDS: Thrombo-embolic deterrent stockings; LMWH: low molecular weight heparin.

### Planning pregnancy /preconception phase

- Assess risk (thrombophilia screen, family & personal history)
- Stop possible teratogenic drugs (3 - 6 months wash-out period)
- Joint care (hematologist / obstetrician)

### Management of an established pregnancy in PV

- FBC every 4 weeks until the 24<sup>th</sup> week and then 2 weekly
- Blood pressure and urinalysis at every visit
- Ultrasound scan at 12, 20, 26, 30, 34 and 38 weeks
- Uterine artery Doppler scanning at 20 and at 24 weeks
- TEDS throughout pregnancy and for 6 weeks after delivery

#### High Risk

- Aspirin 50-100mg/day
- Consider LMWH<sup>1</sup> throughout pregnancy
- Interferon alpha in special situations

#### Highest Risk

- Aspirin 50-100mg/day
- Interferon alpha
- Consider LMWH<sup>1</sup> throughout pregnancy

### Delivery

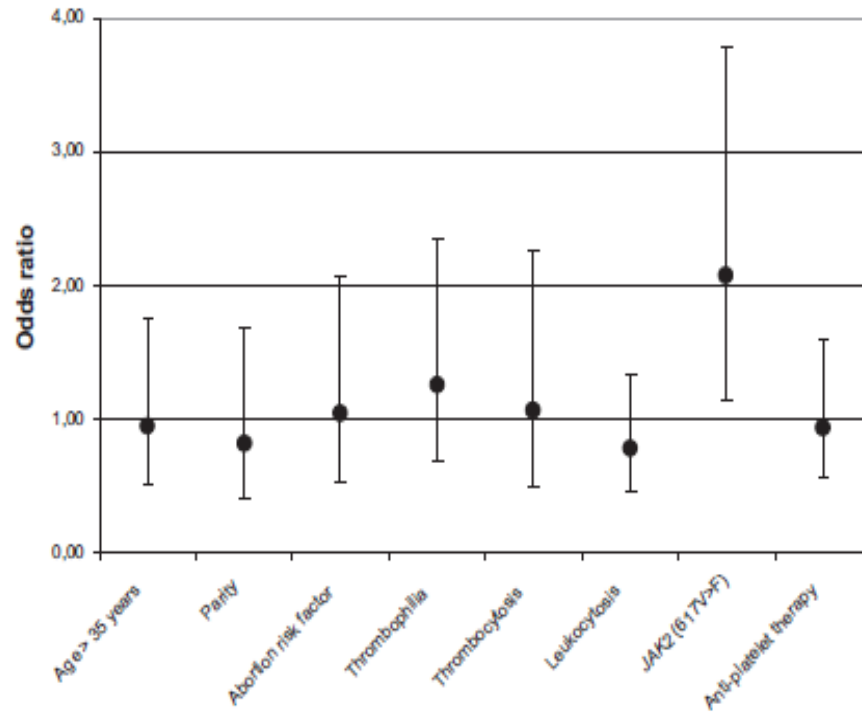
- Consider stopping aspirin 1-2 weeks prior to delivery
- Stop LMWH<sup>1</sup> 12 hours (prophylactic LMWH) to 24 hours (therapeutic LMWH) before labour is expected

### Postpartum

- Restart LMWH<sup>1</sup> + Aspirin for 6 weeks
- Target Hematocrit should be kept in the middle of normal range

**Table 2. Complications of 96 pregnancies in 58 patients with ET**

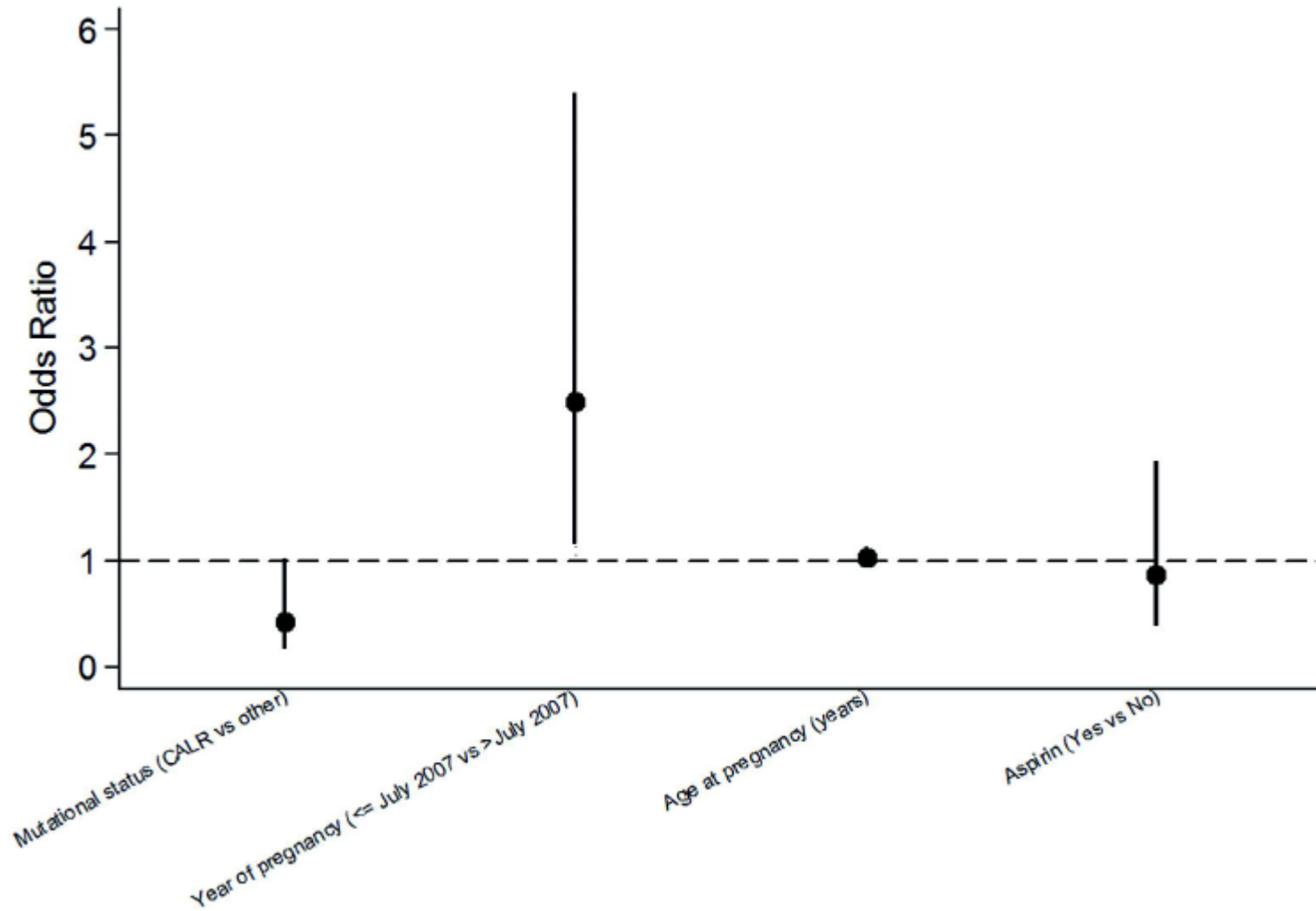
Pregnancy complications	No. of pregnancies (%)
Total events	47 (49)
<b>Fetal loss</b>	<b>34 (36)</b>
First-trimester abortion	27
Second-trimester abortion	4
Stillbirth	3
Intrauterine growth retardation	4 (4)
<b>Maternal complications</b>	<b>9 (9)</b>
Pre-eclampsia	5
Arterial hypertension	4



**Table 1. Distribution of pregnancy complications according to mutational status**

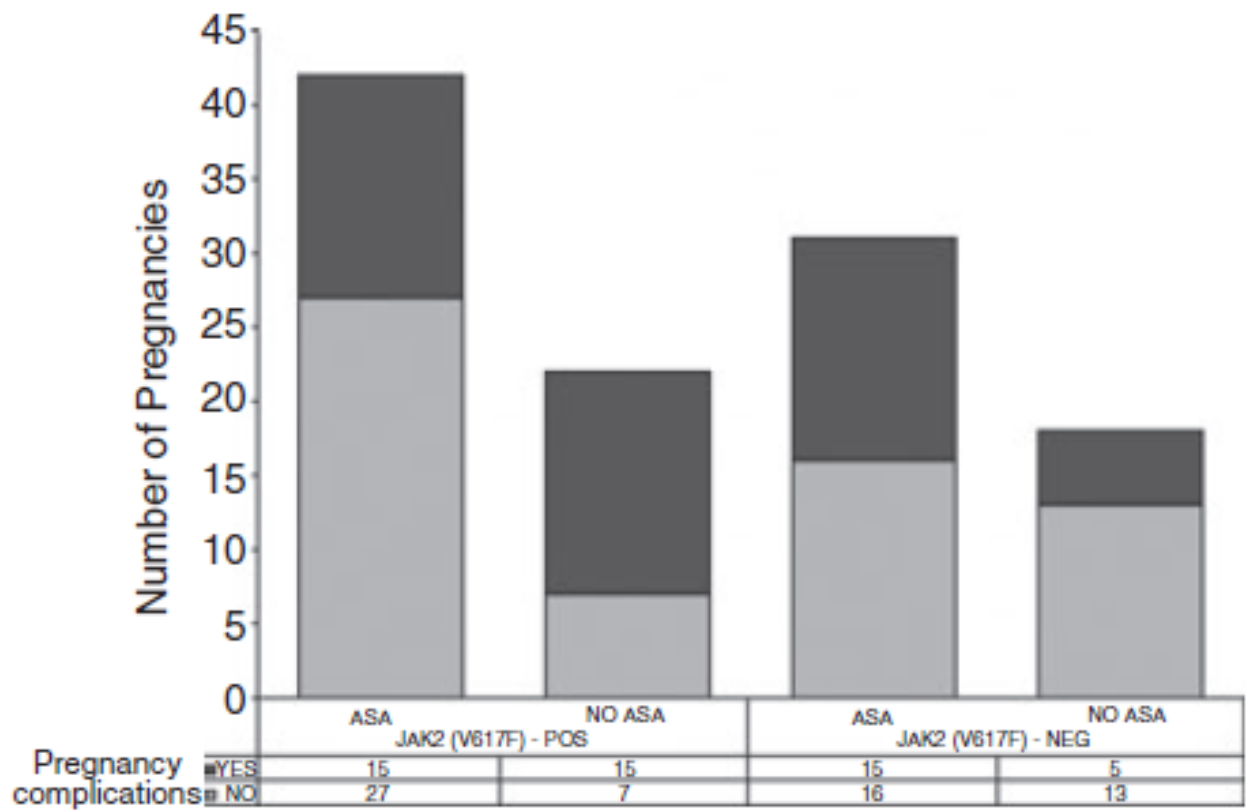
	Mutational status (N° of pregnancies)				<i>P</i> *
	<i>JAK2</i> (96)	<i>CALR</i> (30)	<i>MPL</i> (6)	Triple negative (20)	
<b>Pregnancy outcome</b>					0.810
Full term delivery	52 (54.2%)	19 (63.4%)	2 (33.3%)	13 (65%)	
Preterm delivery	11 (11.5%)	4 (13.3%)	2 (33.3%)	3 (15%)	
First-trimester abortion	24 (25%)	7 (23.3%)	2 (33.3%)	4 (20%)	
Second-trimester abortion	6 (6.2%)	0 (0%)	0 (0%)	0 (0%)	
Third-trimester abortion	3 (3.1%)	0 (0%)	0 (0%)	0 (0%)	
<b>Maternal complications</b>	10/89 (11.2%)	2/30 (6.7%)	2/6 (33.3%)	4/19 (21%)	0.141
<b>Intrauterine growth retardation</b>	7 (7.3%)	1 (3.3%)	2 (33.3%)	3 (15%)	0.064





*Rumi et al, Haematologica 2015*

Is aspirin unuseful ?



**Fig. 1.** Distribution of pregnancy complications according to the *JAK2* (V617F) mutational status and treatment with aspirin. Within *JAK2* (V617F)-positive patients, complications were significantly lower in patients who received aspirin. No significant differences were found among *JAK2* (V617F)-negative patients.

# Outcome of 122 pregnancies in essential thrombocythemia patients: A report from the Italian registry

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**TABLE II. Pregnancy Outcome and Complications in ET Patients**

	All cases	Cases with IFN
<sup>a</sup> Live births	92/122 (75.4%)	19/20 (95%)
Full term deliveries	80	15
Preterm deliveries	12	4
Spontaneous abortions	26/122 (21.3%)	1/20 (5.0%)
≤ 12 weeks	19	1
> 12 weeks	7	0
Still births	4/122 (3.3%)	0/20 (0.0%)
Maternal complications	10/122 (8.2%)	1/20 (5.0%)

<sup>a</sup> The live birth rate was significantly higher in patients treated with IFN during pregnancy than in those who did not receive IFN treatment during pregnancy (19/20, 95% vs. 73/102, 71.6%;  $P = 0.025$ ). The protective role of IFN against fetal loss in ET patients was confirmed in a multivariate analysis (OR: 0.10; 95% CI: 0.013–0.846;  $P = 0.034$ ).

## Pregnancy outcomes in myeloproliferative neoplasms: UK prospective cohort study

*Alimam et al, 2016*

Data obtained from the United Kingdom Obstetric Surveillance System (2010-2012)  
58 women with MPN: 47 ET (81%) , 5 PV (9%), 5 MFI (9%), 1 uMPN (2%)

27 treated with ASA (46%), 24 (38%) ASA + LMWH, 2 (3%) LMWH  
8 (14%) were treated with interferon

56 singleton and 2 twin pregnancies:  
58 live births, 1 miscarriage, 1 stillbirth (fetal loss 1.7%)  
12 neonates (23%) were below the 10<sup>th</sup>

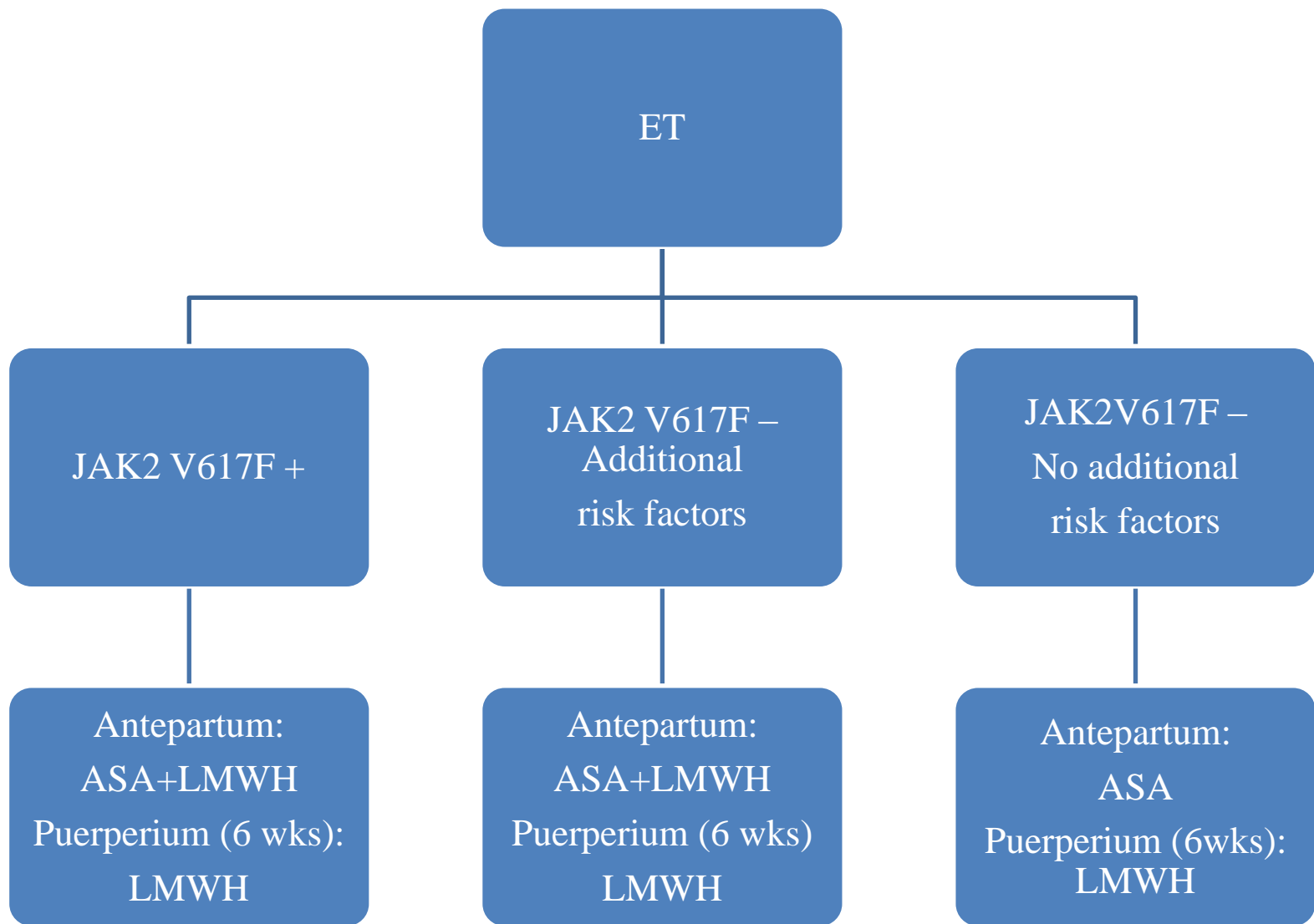
5 preeclampsia (9%)

6 (9%) postpartum haemorrhage

There were no maternal deaths or thrombotic events.

# PROPOSED MANAGEMENT OF PREGNANCY IN MPN WOMEN

Institute of Hematology  
Catholic University, Rome, Italy  
(ambispective study 2001-2014)



- Additional risk factors are age >35 yrs, obesity, thrombophilia
- Cytoreduction with Interferon to keep the platelet count < 400,000/600,000/mmc
- During breastfeeding toxicity is a concern with aspirin due to an association with Reye's syndrome; Ibuprofen can be an alternative, but there is no proof of efficacy in MPN

PV

Antepartum:  
ASA+LMWH  
Puerperium (6 wks):  
LMWH

- Phlebotomies to keep the Htc < 45%
- During breastfeeding toxicity is a concern with aspirin due to an association with Reye's syndrome; Ibuprofen can be an alternative, but there is no proof of efficacy in MPN



	V 617F	WT
JAK 2	V 617F	WT
Women (n)	19	19
Pregnancies evaluable (n)	30	29
Obstetric complications (OC) (n)	13	4
Type of obstetric complications:		
Miscarriage	5	3
Stillbirth	2	0
Abruptio placentae with neonatal death	1	0
Intrauterine fetal growth retardation	5	1

Two of them had hepatic vein thrombosis and TIA before first conception, respectively. One terminated pregnancy, one blighted ovum and one miscarriage due to Turner syndrome were excluded from further analysis.

Women (n)		38	
Pregnancies evaluable (n)		59	
Outcome		Uncomplicated pregnancy	OC
Prophylaxis (pregnancies)	ASA + LMWH (prophylactic dose)	25	7
	ASA	12	2
	LMWH (prophylactic dose)	6	3
	No prophylaxis	2	5

# Results - 1

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- The rate of OC was 43% in pregnancies of JAK2 V617F-positive women (13 / 30) and 14% in the pregnancies of the JAK2 V617F-negative women (4 / 29) (OR 4.77, 95%CI 1.33-17.18)
- However after exclusion of the untreated pregnancies the risk associated with the JAK2 V617F mutation was no more significant (OR 3.33, 95%CI 0.85-13.00).

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## Results - 2

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- A multivariate proportional hazards regression model including age >35 yrs, JAK2 V617F mutation, and antepartum ASA, LMWH, and interferon, retained only ASA as a variable associated with the outcome (OR for complications 0.28, 95%CI 0.10-0.80, p=0.01).
- Among the 6 untreated puerperium periods, one was complicated by cerebral vein thrombosis (17%), whereas no thrombosis occurred during the remaining puerperium periods treated with LMWH.

# Conclusions

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- In ET patients JAK2 V617F is associated with an increased risk of OC, which can be prevented by treatment.
- ASA is effective in preventing ET-related OC; LMWH should be reserved only to women with additional risk factors for venous thromboembolism independent of ET.
- The rate of puerperium-related venous thrombosis is high and prompts LMWH prophylaxis.