Essential thrombocythemia/Polycythemia vera and pregnancy: the need for a observational study in Europe

[1]Martin Griesshammer, [1]Sabine Struve, [2]Claire Harrison

[1]Department of Medicine III, Robert-Koch-Strasse 8, D-89081 Ulm, Federal Republic of Germany, E-mail: martin.griesshammer@medizin.uni-ulm.de, [2]Department of Haematology, Guy´s and St Thomas´ Foundation Trust, St Thomas´Hospital, Lambeth Palace Road, London SE1 7EH, UK, E-mail: claire.harrison@gsst.sthames.nhs.uk,

Correspondence: Professor Dr M Griesshammer, MD, PhD, Department of Medicine III, Robert-Koch-Strasse 8, D-89081 Ulm, Federal Republic of Germany, Phone: 0049-731-5002-4485, Fax: +49-731-502-4405, E-mail: martin.griesshammer@medizin.uni-ulm.de

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Abstract

The management of pregnant patients with essential thrombocythemia (ET) and polycythemia vera (PV) may be problematic. In the literature there are about 300 cases of pregnancies reported in ET and less than 50 pregnancies reported in PV. To reduce the effect of reporting bias we selected papers with either > 10 pregnancies or at least 6 patients and here report on the outcome of 195 pregnancies in ET and 36 pregnancies in PV patients. The live birth rate is approximately 60 % in ET and 58% in PV. Spontaneous abortion during the first trimester is the most frequent fetal complication occurring in 31% of ET pregnancies and in 22 % of PV pregnancies, respectively. Major maternal complications are more frequent in PV compared with ET (44.4% versus 7,7%). Treatment with low dose aspirin during pregnancy in ET seems to reduce complications and also seems beneficial during pregnancy in PV. In high risk pregnancies the additional use of low molecular weight heparin and/or interferon alpha should be considered. In this paper we also present a registry for an observational study concerning pregnancy in chronic Philadelphia negative myeloproliferative disorders within the European LeukemiaNet. We also provide a potential management algorithm for pregnancies in ET or PV.

The chronic myeloproliferative disorders essential thrombocythemia (ET) and polycythemia vera (PV) often present in patients of childbearing potential. In comparison with the other chronic myeloproliferative disorders an increased proportion of women of childbearing age has especially been reported in essential thrombocythemia[1]. The clinical course of ET and PV is determined by a paradoxical predisposition to both major thromboembolic complications and, to a lesser extent, to hemorrhagic problems[2]. Pregnancy itself is a prothrombotic state due to the physiological changes in the coagulation system in preparation of delivery[3]. Additionally, venous blood flow may be decreased by compression of the inferior vena cava and left iliac vein by the gravid uterus. Because ET or PV are associated with a higher incidence of thromboembolic events, a dramatic increase in such complications is potential in pregnancy and they may affect both the mother and the fetus.

In the literature, there are about 300 cases of pregnancies reported in ET and less than 50 pregnancies reported in PV [4-11]. Over 50 % of these pregnancies result in a normal full term delivery, however, there is still a relatively high incidence of various obstetric complications such as recurrent abortion, intrauterine death, premature delivery, fetal growth retardation and preeclampsia[7,9]. As patients have been treated quite differently in the various case reports, no definitive answer can be given on the ideal management for a patient with ET or PV during pregnancy. Idiopathic myelofibrosis (IMF) is least common in patients of child bearing age and the literature comprises only four pregnancies in two patients[1,9,12,13].

In this paper, we briefly review the literature describing pregnancy and its outcome in patients with ET and PV. These results and the limited published data concerning the management of ET or PV in pregnancy clearly demonstrate the need for an observational study perhaps best using established networks within Europe.

Therefore, we present a registry for pregnancies in chronic Philadelphia negative myeloproliferative disorders within the European LeukemiaNet. We also provide a recommendation of a possible management algorithm of pregnancies in ET or PV.

Overview of the literature on ET in pregnancy

Since the first report 1978 of Hoagland and Silverstein on an uncomplicated course of pregnancy in two young women with ET about 300 pregnancies have been reported in women with ET in various case reports[6-10,14-18]. It is important to note, that the available data on ET in pregnancy are both retrospective and variable with regard to management and outcome. Furthermore when single cases or small numbers of pregnancies are reported, there is a tendency to describe patients with complications rather than those with an uncomplicated course. In an attempt to avoid this bias, we have included only reports with either >5 patients or reports with >10 pregnancies in our overview[4-6,10,15,17,19-21]. Thus, we report on a total of 195 pregnancies in 102 women with ET (**Table 1**). Before interpreting these results, it is important to remember, that even in normal pregnancies complications such as spontaneous abortion, stillbirth or premature delivery may occur. The incidence of spontaneous abortion in normal pregnancies is 5 % during the first 12 weeks and then 10 % – 12 % up to the 24th week. Stillbirth (intrauterine death after 24 weeks and infant born showing no signs of life) is observed in about 1 % of all pregnancies. The rate of premature delivery (birth between the 24th and the 37th week or birth weight <2.5 kg) is about 6 %. This amounts to an estimated full-term normal delivery (FTND) rate of about 80 % and a miscarriage rate of 10 % to 15 %[7].

In our literature review the number of pregnancies per patient was 1.9 (195 pregnancies in 102 women). The success rate (baby alive) is 60 % (116 live births in

195 pregnancies). The rate of miscarriage is 40 % (79 miscarriages in 195 pregnancies). The analysis of the various obstetric complications is reported for 179 patients in table 2 (**Table 2**). Details are only given for 179 of the above mentioned 195 pregnancies because only for these pregnancies all the necessary obstetric information are available. A full-term normal delivery (FTND), including forceps delivery or caesarian section, was seen in 49 % (88 of 179 pregnancies). First trimester abortion was the most frequent complication and occurred in 31 % (56 spontaneous abortions in 179 pregnancies). Other complications such as intrauterine death or stillbirth occurred in 6 % (10 of 179 pregnancies) and premature delivery in 8 % (14 of 179 pregnancies). In an earlier review of 155 pregnancies we have previously reported that maternal complications are relatively low in ET during pregnancy[7]. This analysis was restricted to 155 of 195 pregnancies because only for these pregnancies all the necessary maternal information are available. The cumulative incidence of major maternal complications was 5 % for major thromboembolic events (7 of 155, 4 venous and 3 arterial events) and 3 % (5 of 155 cases) for major bleeding (in total 12 of 155 cases, 7.7%). This relatively low rate of maternal complications may be explained by the fact that most affected women belong to the so called low risk group of ET patients with a younger age and a lower incidence rate of thrombotic complications. In some pregnancies of women with ET the platelet count shows a progressive decline during pregnancy, sometimes even to normal levels[7-9]. With an incidence of about 20 % this effect of a decreasing platelet count is well known even in normal pregnancies[22,23]. However, the reduction in platelet counts in pregnant women with ET is greater than the reduction seen in normal pregnancies[7,8,24].

For pregnant patients with ET the various reported treatment options range from no therapy with close observation, antiplatelet therapy with aspirin, heparin or low

molecular weight heparin, to the use of cytoreductive agents. Of course, each therapy has its own risks and possible beneficial effects. In most papers, a positive effect of aspirin on the result of pregnancy has been reported[4,7,8,10,15]. In some ET patients with recurrent spontaneous abortions successful pregnancies were reported after the use of aspirin[4,25,26]. However, the largest series of patients published so far did not provide support for a positive effect of aspirin[17]. Of course, aspirin is contraindicated in patients with a bleeding diathesis, particularly, if the platelet count increases above 1000 x 10^9/l. In these patients with a very high platelet count the risk of bleeding is increased because of an acquired von Willebrand syndrome and this may then be enhanced by the intake of aspirin.

There are a few reports describing the use of heparin in pregnant ET patients. In the largest series reporting the use of heparin, Pagliaro et al. observed superior results in pregnant ET patients after the administration of aspirin and subcutaneous unfractionated heparin (5000 IU every 8 hours) as compared with patients receiving only aspirin or no therapy[15]. In our experience, we also observed a beneficial influence of heparin on the pregnancy outcome in ET patients[4]. However, we used heparin during the last few weeks of pregnancy and in the postpartum period. We stopped low-dose aspirin about two weeks before labour was expected and started with low molecular weight heparin (2500 anti-Xa units subcutaneously once daily). We continued heparin until delivery, with a dose stopped immediately about 12 hours before the expected delivery. Heparin was restarted on the first postpartum day and continued for 6 weeks. As there are no trials evaluating the role of heparin throughout a high risk ET pregnancy, the precise benefit of heparin is unclear. The successful use of low molecular weight heparin (LMWH) in pregnancies with increased thromboembolic risk should however draw attention to its potential use in ET complicated by pregnancy[27-29]. LMWH is safer than unfractionated heparin for it has

a lower risk of heparin-induced thrombocytopenia and osteoporosis. According to a meta-analysis the use of LMWH in pregnancy is a safe alternative to unfractionated heparin as an anticoagulant during pregnancy[30].

In ET patients who require cytoreductive therapy during pregnancy interferon alpha is probably the safest option. Despite the small number of reported pregnancies in ET with interferon alpha, it appears that interferon alpha reduced both ET complications during pregnancy and also has the potential to improve pregnancy outcome[16,31-36]. The use of interferon alpha should be considered in an ET patient with a high risk pregnancy by virtue of:

1. Previous major thromboembolic or major hemorrhagic complications
2. Severe complications in a previous pregnancy despite the use of aspirin ± heparin
3. An increasing platelet count during pregnancy >1000 x 10^9/l.

Interferon alpha is a large molecule and is not expected to cross the placenta barrier in relevant concentrations. There is, however, a report that interferon alpha is probably excreted in breast milk and thus breastfeeding is not recommended whilst using interferon alpha[37].

Because of their potential teratogenic effects other cytoreductive drugs like hydroxyurea or busulfan should be avoided in ET during pregnancy. Particularly during organogenesis in the first trimester of pregnancy these drugs can induce congenital malformation or result in abortion[38]. Even in later pregnancy impaired fetal growth or functional development may result by using these agents. Anagrelide is also not recommended in pregnancy because it may cause fetal harm by crossing the placenta and result in severe thrombocytopenia[9]. Both a normal pregnancy and a spontaneous first trimester abortion have been reported after exposure to anagrelide in early pregnancy[17]. There are a few reports of platelet pheresis in pregnant women

with ET[5,6,39-41]. The platelet lowering effect of platelet pheresis is mostly transient and there is no proof that lowering the platelet count by platelet pheresis always reduces ET related complications in pregnancy. In our opinion, platelet pheresis has a limited role in the management of ET and pregnancy and should only be considered in high risk situations with an excessive increase in platelet count and after an inadequate response to a platelet lowering therapy like interferon alpha therapy.

Overview of the literature on PV in pregnancy

Polycythemia vera (PV) is a disease with a male preponderance and only 15 % of patients are < 40 years or below at presentation[1]. Therefore, compared with the situation in ET, pregnancy in PV is a rarer event. In a recently reported literature review on PV in pregnancy a total of 36 pregnancies have been reported in 18 patients[9]. There was a live birth rate of 58 % (21 of 36 pregnancies). However, three babies out of these 21 live births subsequently had an early neonatal death and thus the surviving neonatal rate was 50 % (18 of 36 pregnancies). Similar to ET, spontaneous abortion during the first trimester was the most frequent complication occurring in 22 % (8 of 36 pregnancies). Late pregnancy loss and intrauterine growth retardation occurred in 19.4 % (7 of 36 pregnancies) and preterm delivery in 13.8 % (5 of 36 pregnancies). In contrast to ET, maternal morbidity was significant. Eight of the reported 18 patients (44.4 %) had significant complications: one death, four pre-eclampsia, two postpartum pulmonary emboli and one large postpartum hemorrhage. In the largest single center series reported so far, 18 pregnancies in eight patients with PV were recently published[11]. Eleven of these 18 pregnancies were managed following a formal protocol and received tailored management principally comprising tight control of the hematocrit by venesection, and aspirin 75mg with six weeks of

LMWH post partum; treatment was escalated to include interferon alpha with LMWH throughout pregnancy in three patients. The remaining seven patients were managed by standard antenatal care without specific attention to the women's PV. In the latter group there was only one live birth whereas in the 11 patients managed with the formal protocol 10 live births resulted. Therefore, it was concluded, that aggressive intervention with control of hematocrit, aspirin, post partum LMWH and in some higher risk cases interferon alpha with antepartum LMWH appears to be associated with a significant better outcome.

European registry of pregnancies in bcr/abl-negative chronic myeloproliferative disorders – The LeukemiaNet project of the European Community

Within the European LeukemiaNet project a registry of pregnancies in bcr/abl-negative chronic myeloproliferative disorders has been implemented in order to document the course and outcome of previous or ongoing pregnancies in these rare diseases. The case reports forms (CRFs) are available via internet

(htttp://www.uni-ulm.de/onkologie/pages/studienzentrale.html#formulare;

password: CMPS_pregnant)

or via e-mail contact with one of the authors (MG/SS). The documentation includes only three CRFs: 1. Information regarding the patient´s chronic myeloproliferative disorder (diagnosis either according to PVSG or WHO), 2. Information regarding previous pregnancies, if any and 3. Information concerning the actual pregnancy. At the moment this is only an observational study, and the process of obtaining ethical approval has yet to be negotiated. Of course, advice will be provided by the authors, if there are any additional problems or questions. A recommendation for a possible

management of either PV or ET in pregnancy is given according to the experience of the authors and the available literature data.

Possible management of ET or PV and pregnancy

The recommendations presented here are based on current knowledge of pregnancy in chronic myeloproliferative disorders and the management of both acquired and inherited thrombophilia and pregnancy. As mentioned above, some experiences of the limited available literature on PV and pregnancy have been described by one of the authors (C.H.). Thus, the suggested management on PV is based on these experiences and the previously described protocol[9,11].

Planning of pregnancy and preconception phase

In principle, pregnancy is not contraindicated in neither ET nor PV and if pregnancy is already established therapeutic abortion is by no means mandatory. Thorough discussions with the mother and father about the problems and complications should take place before a proposal on therapy is made. Patients should ideally be under joint care of a consultant obstetrician experienced in the care of patients with high-risk pregnancies and a hematologist experienced in patients with chronic myeloproliferative disorders. To further assess the risk of thrombotic or obstetric complications, we do recommend to perfom a thrombophilia screening (anticardiolipin antibodies, lupus anticoagulant, factor V leiden, prothrombion mutation, protein C and S, antithrombin, homozygosity for methylenetetrahydrofolate reductase [MTHFR] mutation).

Preconception planning should include cessation of possible teratogenic drugs (hydroxyurea, busulfan, pipobroman). We suggest a three month wash-out period for these drugs. Due to the reasons mentioned above, anagrelide treatment should also be stopped. Alternatively, interferon alpha therapy should be commenced in patients

with a disease-related prior reason for cytoreductive therapy or in high risk pregnancy.

If any of the following factors are present then the **pregnancy is considered at high risk**:

1. Previous maternal major thromboembolic or major hemorrhagic complications
2. Severe complications in a previous pregnancy (≥ 3 first trimester losses or ≥ 1 second or third trimester pregnancy loss, birth weight < 5^{th} 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
3. An increasing platelet count during pregnancy > 1000 x 10^9/l.

Management of an established pregnancy in ET or PV (see Figure 1)

Aspirin: We propose that all patients with ET or PV should be treated with low-dose aspirin (50 to 100 mg/day) throughout pregnancy and for six weeks post-partum. Of course, aspirin is contraindicated, if there is a significant bleeding diathesis or in patients with a peptic ulcer disease. Aspirin could be stopped and substituted by low molecular weight heparin (dalteparin 5000 I.U. or enoxaparin 40 mg once daily) about two weeks before labour is expected.

Low molecular weight heparin (LMWH): In a normal risk pregnancy LMWH is substituted for aspirin in the last two weeks before labour is expected in some centres and then all patients should be treated for six weeks postpartum.

In the following high risk situations low-dose aspirin plus prophylactic LMWH subcutaneously is recommended both in ET and PV throughout pregnancy and for six weeks postpartum:

1. high risk pregnancy as defined above (page 11), or

2. abnormal uterine artery doppler

The presence of two or more hereditary thrombophilic factors (e.g. Factor V Leiden mutation plus a positive lupus anticoagulants) may also be considered as a higher risk pregnancy, however, there are no clear data on this problem neither in ET nor in PV.

In these situations therapy with aspirin and LMWH should start when pregnancy test is positive. Dalteparin 5000 I.U. or enoxaparin 40 mg once daily should be administered, if body weight and renal function is normal. We recommend increasing the dose after 16-20/40 weeks by giving the same dose 12 hourly.

In patients with a previous arterial event, or in order to replace warfarin, or in case of a new thromboembolic event during pregnancy dalteparin 5000 I.U. or enoxaparin 40 mg twice daily should be administered in addition to aspirin.

Interferon alpha: The additional use of interferon alpha should be considered in patients with a disease-related prior reason for cytoreductive therapy or in high risk pregnancy (criteria see above).

Platelet count and hematocrit: Obviously, close monitoring of the blood count is mandatory. We recommend a full blood count (FBC) every 4 weeks until the 24^{th} week and than 2 weekly. Platelet counts should not exceed 1000 – 1500 x 10^9/l because an acquired von Willebrand syndrome is frequently encountered at very high platelet counts and may cause severe bleeding. In PV, the hematocrit should be kept in the middle of the normal range appropriate for gestation with venesection and/or cytoreductive therapy. However, the natural fall of the platelet count and hematocrit may anyway obviate or reduce the need for a therapeutic intervention. In PV, iron supplemetation is not recommended during pregnancy because this may cause an unpredictable rise in hematocrit and may thus increase the risk of thrombosis.

Monitoring of pregnancy - uterine-artery Doppler scanning: Blood pressure and urinanalysis should be performed at every visit. An ultrasound scan is recommended at 12, 20, 26, 30, 34 and 38 weeks. Uterine artery Doppler scanning at 20 and at 24 weeks reveals bilateral notching and indicates a high resitance index as in placental dysfunction. Uterine artery Doppler scanning may identify women at high risk and thus may result in a possible escalation of dose of LMWH. Vitamin supplementation (Vitamin C 1000 mg daily and Vitamin E 400 I.U. daily) is the subject of the VIP (vitamins in pregnancy) study the results of which will be published shortly. Therapy with these supplements should be guided by the results of this study.

Thrombo-embolic deterrent stockings (TEDS): In patients with ET or PV and pregnancy we encourage women to wear TEDS throughout their pregnancy and for 6 weeks after delivery[9].

Delivery in ET or PV

For pain management during delivery, epidural or spinal analgesia is not generally contraindicated in ET or PV. Some obstetric anaesthesists advocate the termination of aspirin therapy one or two weeks prior to delivery. In these situations aspirin could be replaced by heparin. The last dose of heparin should be administered about 12 hours before labour is expected. During labour dehydration should be avoided and the use of thrombo-embolic deterrent stockings should be considered. Regional anaesthetic techniques should not be used until 12 hours after the previous prophylactic dose of LMWH. Following treatment doses of LMWH regional anaesthesia should not be employed for at least 24 hours. LMWH should not be given for at least four hours after the epidural catheter has been removed and the cannula should not be removed within 10-12 hours of the most recent injection[42,43].

For delivery by elective caesarean section, the woman should receive a prophylactic dose of LMWH on the day prior to delivery. On the day of delivery, the morning dose should be omitted and the operation performed that morning. The prophylactic dose of LMWH should be given by three hours post-operatively (over four hours after removal of the epidural catheter, if appropriate).

Postpartum period and breast feeding

It is important to be aware of a persistent ET-related thrombotic and a venous thromboembolic risk extending to the postpartum period. Thus, it is recommended to continue low-dose aspirin and LMWH prophylaxis for at least six weeks postpartum. Discontinuation of aspirin in the postpartum period in ET patients at platelet counts in excess of 400 $x10^9$/l pose a well-documented increased risk of microvascular circulation disturbances including erytromelalgia, transient ischemic attacks, or even hemiparesis[44,45]. The immediate puerperium is indeed the time of greatest risk for venous thrombosis for which prophylaxis with LMWH is indicated. Severe platelet-mediated microvascular disturbances as well as venous thromboembolic complications have been reported in ET post-delivery[44,45]. Rebound thrombocytosis is encountered during the postpartum period and should be controlled by platelet-lowering therapy with interferon, anagrelide or hydroxyurea. This is most important for women who had previously experienced an arterial thrombotic complication.

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Table 1:
Essential Thrombocythemia and Pregnancy: Obstetric outcome reported in the literature
(Reports on > 10 Pregnancies or > 5 Patients)

Reference	Patients	Pregnancies	Live births	Miscarriages
Belluci et al. 1986[15]	3	11	4	7
Beard et al. 1991[5]	6	9	8	1
Leone et al. 1991[16]	8	10	7	3
Beressi et al. 1995[6]	18	34*	17	17
Pagliaro et al. 1996[17]	9	15†	9	6
Randi et al. 1999[18]	13	16	13	3
Bangerter et al. 2000[4]	9	17	11	6
Wright et al. 2001[19]	20	43	22	21
Niittyvuopio et al. 2004[10]	16	40	25	15
Total	**102**	**195**	**116** (60%)	**79** (40%)

* Two elective abortions, one ectopic pregnancy
† One elective abortion

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

Reference	Pregnancies	FTND	SA	SB	PTD	Remarks
Belluci et al. 1986[15]	11	2	6	-	2	1 AP
Beard et al. 1991[5]	9	7	1	-	1	-
Leone et al. 1991[16]	10	7	-	3	-	-
Beressi et al. 1995 [6]	34	15	12	1	2	1 AP, 1EP, 2 EA
Pagliaro et al. 1996 [17]	15	6	2	3	3	1 EA
Bangerter et al. 2000 [4]	17	7	6	-	3	1PoTND
Wright et al. 2001[19]	43	21	16	1	1	1 AP, 1EP, 2 EA
Niittyvuopio et al. 2004[10]	40	23	13	2	2	3 ECL
Total	**179**	**88** (49%)	**56** (31%)	**10** (6%)	**14** (8%)	

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

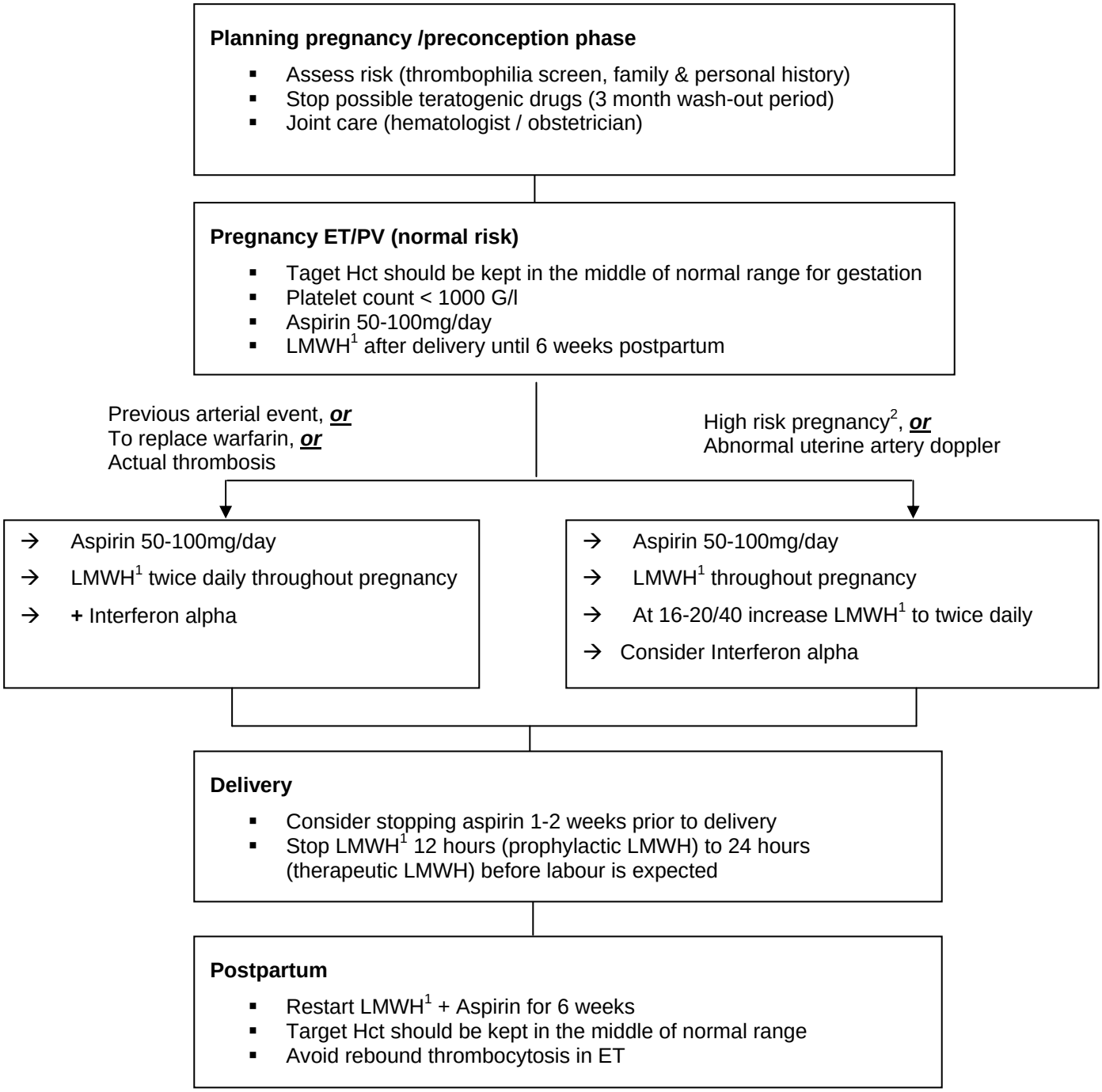

Figure 1: Suggested management algorithm of pregnancy in ET or PV. [1]enoxaparin 40 mg or dalteparin 5000 IU [2]High risk pregnancy: previous maternal major thromboembolic or major hemorrhagic complications, or severe complications in a previous pregnancy, or 3. an increasing platelet count during pregnancy > 1000 x 10^9/l.

Hct: hematocrit; LMWH: low molecular weight heparin