The management and outcome of 18 pregnancies in women with polycythemia vera

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Background and Objectives. Polycythemia vera (PV) is rare in women of childbearing age with only 20 previous pregnancies reported.

Design and Methods. We report a series of 18 pregnancies (19 fetuses) in eight women with PV managed prior to or following implementation of management guidelines tailored to PV in pregnancy, and review the literature.

Results. Seven of these pregnancies were managed by standard antenatal care (group A) without specific attention to the women's PV. All remaining 11 pregnancies (group B) were managed following a formal protocol and received tailored management principally comprising tight control of the hematocrit by venesection, and the use of interferon α in three patients, in addition to aspirin 75 mg, and prophylactic low molecular weight heparin (LMWH). Each pregnancy was monitored with uterine artery Doppler examinations and regular fetal scanning. In group A (n=7) there was one live birth, which required delivery at 34 weeks due to placental insufficiency, three first trimester miscarriages, two stillbirths and one combined stillbirth and neonatal death (twins) associated with placental dysfunction. All 11 patients in group B received aspirin and post-partum LMWH; four also received venesection (during pregnancy), three interferon-α and three antenatal LMWH. There were ten live births, nine at term, one first trimester miscarriage and no intrauterine growth retardation.

Intepretation and Conclusions. Pregnancy in PV without meticulous attention to hematocrit is associated with poor fetal outcome. Aggressive intervention with control of hematocrit, aspirin and some LMWH appears to be associated with significantly better outcome (*p*=0.0017).

Key words: pregnancy, polycythemia vera.

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Polycythemia vera (PV) is a clonal myeloproliferative disorder of hematopoietic stem cells, characterized by an increase in red cell production. The mean age of diagnosis is 60 years, but 15% of cases are diagnosed in people under 40 years old. The incidence in women increases during the reproductive years (from 0.04 per 100,000 in those aged 20-34 years to 0.25 per 100,000 in those aged 35-39 years) and peaks at 65-69 years (1.84 per 100,000).[1] Clinical complications include venous and arterial thrombosis, hemorrhage, and in the long-term, transformation to myelofibrosis or acute myeloid leukemia.

Normal uterine blood flow and adequate placental growth are key to a successful pregnancy outcome. In the first and early part of the second trimester of pregnancy the embryonic trophoblast invades the endometrial capillaries and then the spiral arteries[2] and the placenta develops. The consequences are conversion from a low volume, high resistance circulation to a high volume, low resistance circulation. Failure of conversion can be detected by uterine artery Doppler scanning[3] and may be the earliest marker of placental dysfunction. When compared to normal fetuses, those with intrauterine growth retardation (IUGR) have been shown to have a four-fold reduction in uteroplacental blood flow.[4] Other severe pregnancy complications such as placental abruption and pre-eclampsia are also associated with uteroplacental dysfunction.

Placental dysfunction is known to occur in some other acquired and inherited causes of thrombophilia. Antiphospholipid syndrome is perhaps the best example of an acquired thrombophilia in which an active intervention leads to improved pregnancy outcome.[5,6]

The most extensive literature relating to pregnancy in myeloproliferative diseases exists for essential thrombocythemia (ET) with over 280 pregnancies reported in 147

patients. There have been a number of reviews that have analyzed these cases[7-10] and demonstrate significant fetal complications. Overall there is a successful live birth rate of 50-57%. First trimester loss is the most common complication in 26-36%; the expected rate of spontaneous abortion in pregnancy is 15-20% and three or more losses occur in 1-2%.[11,12] Late pregnancy loss is also more prevalent in ET; 5-9.6% of pregnancies end in this way among women with ET compared to 0.5% for the normal population.[12,13] Furthermore, in ET pregnancies IUGR occurs in 4-5.1%, preterm delivery in 5.6-8%, and placental abruption in 2.8%. Placental thrombosis has been documented in ET pregnancies complicated by late fetal loss,[14] pre-term delivery[14] and IUGR.[15] Maternal complications are relatively rare and no fatal events have been documented. Thrombosis is most common and usually minor, but major thrombotic events have also been reported including cerebral sinus thrombosis, deep vein thrombosis and transient ischemic attacks.[8,10] The apparent low risk of maternal complications should be considered in context as the majority of these patients would be viewed as *low risk* for general ET management, suggesting that pregnancy does increase the risk of thrombosis as would be anticipated. Disappointingly, the literature on ET does not facilitate identification of risk factors for pregnancy-related events nor does it indicate a clear therapeutic strategy.

However, given the expanding literature on antithrombotic therapy in successful pregnancy management in both antiphospholipid syndrome and/or inherited thrombophilia, it would appear logical to offer similar therapeutic strategies in ET. Therapeutic options in ET also include cytoreductive drugs such as hydroxyurea (also known as hydroxycarbamide), anagrelide and interferon-α. Based on an uncontrolled retrospective analysis of 25 ET patients it appears that interferon-α therapy reduced both ET complications during pregnancy and also apparently improved pregnancy outcome.[10,16-22] It has also been suggested that treatment with hydroxyurea facilitated successful pregnancy outcome in one patient with a history of two stillbirths in the third trimester.[23] This suggests that cytoreductive therapy might potentially protect against fetal loss, but with such small numbers such a conclusion remains unproven.

We report the outcome of 18 pregnancies in eight women with PV seen in our institution. A detailed review of the literature on pregnancy in PV is presented in the discussion.

Design and Methods

Our Hematology department has a specialist myeloproliferative clinic. Patients with a diagnosis of PV who attend this clinic and are attempting to conceive, or are known to be pregnant, are reviewed by a consultant with a specialist interest in myeloproliferative disorders and an obstetrician experienced in the management of high-risk pregnancies. Further patients from colleagues at other hospitals are referred for specialist advice regarding pregnancy and are either managed locally with monthly specialist review or in complex cases followed up and delivered within our institution.

Our protocol for the management of pregnancy in ET and PV[24] states that if any of the following factors were present then the pregnancy was considered at high risk of complication to the mother and/or fetus: previous venous or arterial thrombosis or hemorrhage attributed to myeloproliferative disease; previous pregnancy complication (>3 first trimester losses or >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 platelet count rising to >1,500×10⁹/L. Preconception planning included cessation of possible teratogenic medications, advice on a *wash-out period*, and precise control of PCV pre-pregnancy. Interferon-α was commenced in those with a disease-related prior reason for cytotoxic therapy or in high-risk pregnancies (as defined above). The target PCV was initially less than 0.45 though this was subsequently modified to be compatible with a mid-gestation appropriate range. All patients received aspirin (75 mg) and prophylactic LMWH for six weeks post-partum. Treatment details are provided in Table 1. Uterine artery Doppler studies were performed at 20 and 24 weeks[3] in all pregnancies to obtain an assessment of placental function. If bilateral notching was detected then escalation of therapy including the addition of antioxidant vitamins C and E and dose escalation of LMWH was considered (the former now in the context of the Vitamins in Pregnancy-VIP-randomized controlled trial). It was advised that fetal growth monitoring was performed at least every 4 weeks, or more frequently according to the progress of the pregnancy. In view of the known associations of thrombophilia with pregnancy morbidity[25] and risks of venous thrombosis, a comprehensive thrombophilia profile for all patients was obtained, usually preconception.

Data were compiled retrospectively from medical and obstetric records. Further information was requested from patients, referring institutions and physicians, in particular with reference to previous pregnancies. Details of diagnosis, thrombophilia screening, previous obstetric history, hematologic indices, treatment and outcome of each of the 18 pregnancies were collected for data analysis. The patients were divided into group A, comprising patients who received standard antena-

Table 1. Details of 18 pregnancies in polycythemia vera.

Patient	Pregnancy	Age (years)	Treatment Group	IUGR	Outcome
1	1	17	Prediagnosis		TOP
	2	20	Prediagnosis	Yes	IUGR, oligohydramnios Elective Cesarean section
	3	21	Prediagnosis		SVD FT
	4	24	Prediagnosis		SVD FT
	5	32	B Venesection Fragmin 5000u bd s/c 8/40 onwards		Query PE 8/40 SVD FT
2	1	34	A	Yes	Hypertensive, fetal distress, emergency CS 34/40 (1504 g) IUGR. Placental insufficiency, infarcted small placenta
3	1	36	A		Misc (1ˢᵗ trimester)
	2	38	B		SVD FT
4	1	18	Prediagnosis		TOP
	2	20	Prediagnosis	Yes	30/40 SVD Pre-eclampsia (1362g) IUGR
	3	21	Prediagnosis		TOP fetal abnormality
	4	23	A		Misc 7/40
	5	23	A		Misc 11/40
	6	24	B		Elective CS 38/40
	7	28	B		Misc (1ˢᵗ trimester)
	8	30	B IFNα preconception Enoxaparin 40 mg od post partum		Elective CS 38/40 3600g
5	1	30	A	Yes	Pre-eclampsia, IUGR, oligohydramnios, SB 25/40 (450g)
	2	31	A	Yes	Pre-eclampsia, IUGR 25/40. Twin 1, IUD Twin 2, Neonatal death
	3	37	B IFNα Enoxaparin 40 mg od until 20/40 then bd Vit C & E		SVD FT
6	1	32	B Venesection		SVD FT (3900g)
	2	37	B		Elective CS FT (4200g)
7	1	31	B Venesection		33/40 SVD
	2	33	B IFNα Venesection		SVD FT
8	1	29	A		IUD 29/40 placental infarction
	2	31	B IFNα Enoxaparin 40 mg od until 20/40 then bd		SVD 38/40 3500g

Group A standard antenatal care. Group B managed according to protocol. TOP: termination of pregnancy; SB: stillbirth; SVD: spontaneous vaginal delivery; FT: full term; IUGR: intrauterine growth restriction; IUD: intrauterine death; CS: Cesarean section; Misc: miscarriage; PE: pulmonary embolism; IFNα : interferon α; LMWH: low molecular weight heparin.

tal care with no manipulation of blood counts (either by venesection or cytotoxic therapy), no heparin or aspirin, and group B, comprising the patients treated according to our protocol. The results were compared according to management in pregnancy and to those cases reported in the literature. Fisher's exact test was used with Unistat 5.0 (London) software.

Results

We identified 18 pregnancies (19 fetuses) occurring in eight women age 17-38 years with a diagnosis of PV according to World Health Organization criteria. None of these patients had a recognized throm-

bophilic abnormality other than PV. The data from this case series are summarized in Table 1 and confirm a significant fetal morbidity in PV with only 11 live births, four first trimester losses, three stillbirths and one neonatal death. Overall there were three cases of IUGR and three premature births at 34, 36 and 26 weeks. Maternal morbidity in this case series was minor. One patient had an unconfirmed pulmonary embolus at eight weeks (suggestive history but inconclusive ventilation perfusion scan), and there were three cases of pre-eclampsia (patient #4, and two early pregnancies of patient #5 in the standard care group A).

In group A there was only one live birth in a pregnancy complicated by placental insufficiency and IUGR, and seven fetal deaths comprising three first trimester losses, one neonatal death and three stillbirths (two of which were complicated by IUGR and one by placental infarction). By contrast, there was only one unsuccessful outcome in the actively managed pregnancies (group B). Nine out of ten live births were full term. The difference in rates of live births between these two groups was statistically significant (p=0.0017, Fisher's exact test) despite the small numbers involved. Unfortunately analysis of the influence of prior pregnancy events, platelet counts or packed cell volume (PCV) on pregnancy outcome was limited by patient numbers.

Pregnancies occurring prior to a diagnosis of PV were considered separately (Table 1), but a significant incidence of complications is also apparent. There were seven pregnancies prior to PV diagnosis. Two out of four live births were complicated by IUGR (one of the two also had pre-eclampsia) necessitating early delivery and the other two live births were uncomplicated; there were three elective terminations of pregnancy. Blood counts available for these pregnancies were normal.

Discussion

Pregnancy is a prothrombotic state and confers a greater risk of venous thromboembolism especially in patients with thrombophilia for whom there is also evidence of an increased risk of adverse pregnancy outcome. For patients with PV thrombotic events (both venous and arterial) dominate the clinical phenotype and are the significant predictors of prognosis.[26] The risks associated with pregnancy in PV are unclear. The previous literature (excluding three texts with insufficient detail)[27-29] comprises nine reports of 20 pregnancies,[30-38] with no author reporting more than two patients or four pregnancies. The obstetric outcome and complications documented in these papers are outlined in Table 2. There were 11/20 (55%) live births

although three resulted in early neonatal death reducing the overall success rate to 8/20 (40%) healthy neonates. The treatments these patients received during pregnancy were highly varied. Only 10 of the 20 pregnancies received some PV-related management, with two receiving aspirin during pregnancy and 6 weeks of heparin post-partum, mirroring our active therapy. Most of these patients were managed before 1983 and the PCV was not aggressively controlled. Historical management perhaps reflects the level of knowledge at that time, since the Polycythaemia Vera Study Group, which significantly informed management of this disease, was only founded in 1967, and ten of these pregnancies predate 1968.

The 18 pregnancies reported here significantly expand the available literature in this field and we have been able to compare maternal and obstetric outcome before and after introduction of a well-defined pregnancy management protocol already presented in detail elsewhere.[24] Overall there were 11 live births, four first trimester losses, three stillbirths and one neonatal death (19 fetuses), three cases of IUGR and three premature births at 34, 36 and 26 weeks. Maternal morbidity in this case series was minor. One patient had an unconfirmed pulmonary embolus at eight weeks (suggestive history but inconclusive ventilation perfusion scan), and there were three cases of pre-eclampsia. Subanalysis suggests that those patients treated according to our protocol had a significantly better outcome (1/7 vs 10/11 live births, p=0.0017) although the numbers involved are small.

When our own case series is combined with historical cases, there is a live birth rate of 22/38 (57%), although the rate of surviving neonates is only 19/38 (50%). In common with ET, first trimester loss is the most frequent complication (8/38, 21%), followed by late pregnancy loss and IUGR (6/38,15%) and preterm delivery (5/38,13%). If all 38 pregnancies including literature review cases and the present case series are assigned to either group A or group B according to review of management in individual cases (Table 2), the analysis of the benefits of active management versus traditional antenatal care still suggest active individually tailored management (control of PCV<0.45, aspirin and post-partum LMWH; group B) is of statistically significant benefit (p=0.012, Fisher's exact test)

The possibility that our management strategy improves pregnancy outcome is confounded by small numbers, and the fact that comparisons are made with historical controls (previous literature and pregnancies in case series group A). It is likely that the major component of this improvement is related to meticulous attention to the PCV with a contribution from daily aspirin and post-partum LMWH. Furthermore the significant literature favoring active antithrombotic therapy in improving fetal outcome in pregnancies affected

Table 2. Reported cases of pregnancy in patients with polycythemia vera.

Author	No. of pts.	No. of Pregnancies	Previous thrombosis	Previous hemorrage	Treatment pre-pregnancy	Treatment during pregnancy	Treatment group	High risk	Maternal outcome	Live birth total	Pregnancy loss total	Misc 1st trimester	Still birth	IUGR	Live birth premature delivery <37/40	Live birth FTD
Crowley 1987	1	1	No	No	Aspirin + dipyrimadole	Aspirin + dipyrimadole	A	No	Death*	0	1	1 TOP	0	0	0	0
Centrone	1	3	No	No	Nil	Nil	A	No	Alive	1	2	2	0	0	0	1
Ferguson 1983	1	2	No	No	Venesection	Nil	A	No	Alive PET	2	0	0	0	0	0	2 PET
Ruch 1964	1	2	Superficial thrombophlebitis	No	Venesection and ^{32}P	None	A	No	Alive PET	1	1	0	1@35/40 & PET	1	0	1
Subtil 2001	1	3	No	No	Venesection	Aspirin, heparin** venesection	B	No	Alive PE post partum	1	2	0	***2 @24 & 28/40	2	1 32/40	0
Hochman 1961	1	4	Yes, CVA	No	Venesection TBI prior to third pregnancy	Nil	A	Yes	Alive PET	2	2	0	2 (5+7 months) PET	0	1@7 months PET 1@8 months	0
Harris 1967	2	2@	No	No	Nil	Nil	A	No	Alive PPH	2@	0	0	0	0	0	2
Ruggeri 2001	1	2	No	No	Venesection + aspirin	Heparin 3/52 post partum	A	No	Alive, PE 24/7 post partum	1	1	1	0	0	0	1
Pata 2004	1	1	No	No	Hydroxyurea	Hydroxyurea 9/40 then nil	A	No	Alive	1	0	0	0	0	0	1
Current series see Table 1	8	18 (1 twin)	Yes (1 patient)	No	Venesection, Aspirin, Interferon, Hydroxyurea	Varied: Venesection, Aspirin, Interferon LMWH, vitamin C+E	A=7 B=11	10/18	Alive PET in 1	11	7	4	2	3	1 34/40IUGR 1 36/40 1 26/40NND	9
Total	18	38 1 thrombophlebitis	1 CVA	None					1 death 4 PET 2 PE 1 PPH	22 3 NND	16	8	7	6	6	17

Misc: miscarriage; IUGR: intra-uterine growth retardation; FTD: full term delivery; NND: neonatal death; TOP: termination of pregnancy; PPH: post partum hemorrhage; PET: pre-eclampsia; LMWH: low molecular weight heparin. Treatment: group A standard antenatal care, group B PV specific therapy. *the patient died with evidence of deep vein thrombosis, pulmonary emboli, saggital sinus thrombosis, and disseminated intravascular coagulation. ** aspirin and post-partum heparin in second pregnancy, LMWH and aspirin throughout third pregnancy. *** multiple placental infarcts in first, and abnormal Doppler waveforms and severe IUGR in third pregnancy, @one singleton and one twin pregnancy (this patient had previously had a twin pregnancy terminating in intrauterine death at 22 weeks, followed by two normal pregnancies and then the diagnosis of PV).*

by inherited thrombophilia and anti-phospholipid syndrome may have some relevance to fetal outcome in PV.[39-41]

Maternal morbidity due to thrombotic and bleeding problems were notable in the previous reports with one death due to disseminated intravascular coagulation and venous thromboembolism after an elective termination of pregnancy; two post-partum pulmonary emboli, and one large post partum haemorrhage. In the current series the only maternal morbidity was a possible but unconfirmed pulmonary embolus (patient 1)

and three cases of pre-eclampsia, all in pregnancies not intensively managed for PV (group A).

The ECLAP study[42] supports the widespread use of low-dose aspirin in PV. The safety of aspirin in pregnancy is substantiated by the CLASP study.[43] The pathogenesis of thrombosis in PV is not identical to that in other prothrombotic states and is due in the most part to blood rheology as determined by PCV and to a lesser extent, by leukocyte adhesion, platelet activation, and platelet – leukocyte aggregates.[44,45] In the absence of antithrombotic therapies specifically

targeted to these areas it seems reasonable to utilize aspirin and LMWH as adjuncts to strict control of the PCV. Indeed, whether the use of LMWH added to aspirin is of benefit to fetal outcome in PV is uncertain from an analysis of this case series. However, LMWH has been shown to be superior to aspirin in improving fetal outcome in women with a previous pregnancy loss and thrombophilia (factor V Leiden, protein S and prothrombin gene mutation),[40] supporting our decision to use LMWH in high risk pregnancies not just in patients with prior thrombotic events.

More speculative elements of our protocol are the use of interferon-α and/or the antioxidant vitamins C and E. Interferon-α was introduced based on reports of its successful use in ET.[10] For those PV patients who require cytoreduction prior to conception the choice of interferon-α is logical as it is the cytoreductive drug that appears least harmful to the fetus. More controversial is the use of interferon-α for patients (such as patients #5 and #8) whose disease might not warrant cytoreduction but who have had significant prior serious pregnancy complications. Here therapy is based upon the suggestion that thrombosis underpins the utero-placental dysfunction that resulted in past pregnancy complications. This was documented on histological examination of the placenta. In the non-pregnant state control of myeloproliferation or cytoreduction for PV has been documented to reduce the incidence of thrombosis significantly[46-48] hence supporting the aggressive control of PCV (with either interferon-α or venesection) and platelet count in such patients.

Interest in the use of anti-oxidants in pregnancies at high risk of pre-eclampsia is derived from the Vitamins In Pre-eclampsia study. This double-blind, randomized study showed that supplementation with antioxidant vitamins C (1000 mg/day) and E (400 IU/day) reduced the incidence of pre-eclampsia significantly in the treated arm.[49,50] A larger multi-center study on the use of anti-oxidants in the treatment of pre-eclampsia is currently underway.[51] The biological basis for their possible benefit relates to a two-stage theory, which suggests that placental dysfunc-

tion is the root cause and that free radicals produced by the placenta cause the maternal signs of pre-eclampsia by activating maternal endothelium.[51] Thus the logic of using antioxidants is that they will bind to the free radicals, preventing maternal signs. There is currently no clear evidence for the role of antioxidant vitamins in patients with myeloproliferative diseases (patient #5 was the only patient who received antioxidant vitamins) and the present protocol includes participation in the VIP multicenter study).[51] Interestingly, the pregnancies documented prior to a diagnosis of PV in our patients also appear to have had a poor outcome which may reflect pre-clinical disease with masking of abnormal blood counts by the known hematologic effects of pregnancy. It is well known that patients with PV and other myeloproliferative diseases have an increased risk of thrombosis prior to diagnosis.[52] Hence careful review of the blood count in any woman with a pregnancy complication is appropriate to exclude a myeloproliferative disorder.

In conclusion, pregnant women with PV have an increased risk of fetal loss through all trimesters, IUGR, prematurity and poor fetal outcome. This largest series of patients to date supports the use of therapies tailored according to previous disease and prior pregnancy complications. As PV is a rare clinical condition international and prospective collaboration is required to investigate this matter further.

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