Pegylated interferon alpha-2a for essential thrombocythemia during pregnancy: outcome and safety. A case series

Pregnant woman with essential thrombocythemia (ET) are at higher than normal risk of pregnancy complications. Current recommendations suggest that aspirin and cytoreductive therapy should be offered for high-risk pregnancies but Pegylated interferon alpha-2a (PEG-IFN) has never been investigated in this context. From our case series, including 10 pregnancies, we demonstrate that PEG-IFN has been well-tolerated, allows reduction and control of platelet count during pregnancy, and is associated with a high live birth rate (90%) and low miscarriage rate (10%).

Essential thrombocythemia (ET), a myeloproliferative neoplasm, is a rare disease with an estimated incidence of 0.38-1.7/100,000 per year.[1] Peak incidence is during the sixth decade; however, up to 20% of patients are diagnosed before the age of 40 years.[2] The main risks associated with ET are thrombosis and hemorrhage, the respective prevalence of which in young women is 18% and 26%.[3] Patients older than 60 years and/or with previous history of thrombosis and /or with platelet count greater than 1500x10^9/L are considered to be at high risk of thrombotic events and cytoreductive treatment is generally recommended[4] as a consequence. Previous descriptive studies of pregnancy in women with ET suggested a risk of first trimester miscarriage of 27% with a live birth rate of only 64%.[5] Data currently available on pregnancy outcome in ET are based on retrospective cohorts, and the impact of variables including presence of *JAK2*V617F, prior pregnancy complications, therapy, high leukocyte count and platelet count are contradictory. A recent study showed a trend towards better outcome for patients harboring CALR mutations.[7] The benefit of low-dose aspirin (ASA) is contradictory, with some studies suggesting a reduction of miscarriage in treated patients[6] and others not.[8] However, safety of ASA in this population is well established.[9] Currently, interferon alpha (IFN) and PEG-IFN are not approved for ET and pregnancies and should be used in pregnancy only if benefits justify the potential risk to the fetus (category C). However, one retrospective study reported safety for IFN-treated pregnant patients with an increase in live birth rate,[8] and current recommendations consider IFN as a reasonable treatment.[4] There are currently no data relating the safety and efficacy of PEG-IFN in pregnant ET patients. Only one case of pregnant ET[10] and anecdotal use of PEG-IFN in different pregnancy scenarios (CML, hepatitis) have previously been reported. For this reason, PEG-IFN is currently not recommended for pregnant ET patients.

In this observational study, we included pregnant women with a diagnosis of ET treated with PEG-IFN with pregnancy outcome available. Patients were identified by physicians who agreed to participate in the study. Five centers in the UK (Guy's and St. Thomas' NHS Foundation Trust, London; St James's University Hospital, Leeds; University Hospital of Wales, Cardiff; Beatson West of Scotland Cancer Centre, Glasgow; Countess of Chester Hospital, Chester) participated in this study. PEG-IFN was used off label and initiation of other drugs (e.g. ASA, LMWH) reflects the choice of the treating physician. Demographics, past medical and obstetric history, previous thrombosis and hemorrhage, previous treatment, disease characteristics at diagnosis and during pregnancy were retrospectively extracted from patients' notes. This study was performed in accor-

Table 1. Patients' characteristics; n=10 pregnancies in 8 women.

Pt. n.	Age at diagnosis	PLT count at diagnosis	Obstetric history*	Thrombosis history	Age at conception (years), on PEG-IFN	Pregnancy outcome	Gestation at pregnancy outcome (weeks+days)	Birth-weight	Maximum PEG-IFN dose during pregnancy	Concomitant treatment during pregnancy	Median PLT count during first trimester (x10^9/L)	Median PLT count during second trimester (x10^9/L)	Median PLT count during third trimester (x10^9/L)
1	34	791	1 LB	None	39	LB	40+0	3.1	90 µg e1w	ASA, LMWH pd	346	306	262
2	33	702	1 LB, 3 MC	Sagittal thrombosis	39	LB	39+1	3.1	135 µg e5w	ASA, LMWH td	254	225	183
3	22	1600	None	None	24	MC	6+0	NAp	45 µg e1w	ASA	512	NAp	NAp
3	22	1600	1 MC	None	25	LB	38+3	4.1	45 µg e1w	ASA	434	435	370
4	18	2000	1 MC	None	24	LB	40+6	3.7	45 µg e1w	ASA, LMWH pd	265	N/A	333
5	12	3265	1 TOP	None	21	LB	38+4	2.8	270 µg e1w	ASA	570	454	428
6	23	1693	1MC	None	33	LB	39	3.1	90 µg e1w	ASA, LMWH pd	446	469	350
6	23	1693	1LB, 1MC	None	36	LB	42	3.2	90 µg e1w	ASA, LMWH pd	442	393	288
7	30	664	1 LB	Portal vein thrombosis	34	LB	39	2.5	45 µg e2w	LMWH td	223	220	217
8	23	960	None	None	31	LB	40	3.1	135 µg e1w	ASA	612	473	467

*Pt: patient; ASA: aspirin; e1w: every 1 week; e2w: every 2 weeks; e5w: every 5 weeks; LB: live born; LMWH: low-molecular weight heparin; MC: miscarriage; N/A: not available; NAp: not applicable; PLT: platelet; pd: prophylactic dose; td: therapeutic dose; TOP: termination of pregnancy. *Obstetric history included all outcomes of prior pregnancies. Patients 3 and 6 had 2 pregnancies on PEG-IFN. Therefore, obstetric history is different between the two pregnancies: the obstetrical history of the second pregnancies includes outcome of the first one.*

dance with the Declaration of Helsinki. Patients' characteristics were reported descriptively. Categorical variables were expressed as proportions and continuous variables as the median with the range. Nominal variables were compared with Fisher's test. Comparison of dependant variables were analysed by Friedman test. Two-sided $P<0.05$ was considered significant. Objectives were to describe pregnancy outcomes including live birth, fetal loss, birthweight, mode of delivery, gestation at delivery; efficacy (platelet count during pregnancy) and tolerability of PEG-IFN during pregnancy.

The study included 10 pregnancies in 8 women observed between 2013 and 2015. In all cases, the diagnosis of ET had been made prior to pregnancy. Median age and median platelet count at diagnosis were 23 years (range 12-34 years) and 1280x10^9/L (range 664-3265x10^9/L), respectively. At diagnosis, 6 (75%) patients were considered high risk (4 with platelet count >1500x10^9/L and 2 with history of thrombosis: 1 sagittal vein thrombosis and 1 portal vein thrombosis). Five (63%) were *JAK2*V617F positive. Comprehensive details of mutational status were not available for the remaining patients. Six women (75%) had a prior documented history of 9 pregnancies without PEG-IFN with 3 (33%) live births, 5 miscarriages (56%) and one voluntary termination of pregnancy (11%). During the 5 pregnancies that resulted in miscarriages, all women were on ASA, one on low molecular weight heparin (LMWH), and one on IFN. Of the 3 previous live births, one mother received ASA alone and experienced neurological symptoms with right hemi-facial and upper limb numbness during pregnancy, and the neonate was of low birth weight and placental histology suggesting insufficiency; one was on IFN, and therapeutic dose LMWH following prior thrombosis complications included a placental hemorrhage and perineal hematoma; and one was on ASA and prophylactic dose of LMWH (delivered without any complication). Median age during pregnancy with PEG-IFN was 32 years (range 21-39 years). PEG-IFN was started before conception in all women. In addition to PEG-IFN, all but one woman (the case with previous portal vein thrombosis on long-term anticoagulation) were on ASA and 5 (63%) of them were on LMWH [3 (38%) on prophylactic dose and 2 (25%) on therapeutic dose for previous thrombosis]. The rationale for the introduction of cytoreductive treatment was high-risk ET for 6 women (75%), ET-related symptoms in one (13%), and complications in previous pregnancy in one woman (13%). Median dose of PEG-IFN was 270 mcg/month (range 90-1080 mcg/month). Five woman experienced PEG-IFN grade 1 adverse events (AEs) (2 reported hair loss, one had mild mood swing, one had fatigue, one had transient nausea, anorexia and abdominal pain, one had a skin reaction, one had headaches) and one had grade 2 AEs (neutropenia). Neither grade 3-4 AEs nor drug discontinuation was reported. There was a significant reduction in the platelet count during pregnancies managed with PEG-IFN ($P<0.05$). Median platelet count at conception was 509x10^9/L (354-676x10^9/L), 438x10^9/L (range 223-612x10^9/L) during the first trimester, 414x10^9/L (range 220-473x10^9/L) during the second trimester, 333x10^9/L (range 183-467x10^9/L) during the third trimester and 285x10^9/L (range 172-460x10^9/L) at delivery.

Of the 10 pregnancies, all were singleton. Nine (90%) resulted in live birth and one (10%) in miscarriage (at 7 weeks, platelet count 492x10^9/L). Median time of gestation at delivery was 39 weeks (range 38+3-42 weeks) and median birthweight was 3.1 kg (range 2.5-4.1 kg). Delivery was vaginal for 8 (89%) and by caesarean section for one (11%) (breech presentation), with induction of labor for 2 (22%). Neither major bleeding nor thrombosis were reported during pregnancy, delivery or post-partum. There were neither stillbirths nor infant malformations. Finally, when comparing outcomes of pregnancies of these 8 women on PEG-IFN or without (after having excluded 1 voluntary termination of pregnancy from the analysis), there were significantly more live births on PEG-IFN (*9 vs.* 3; $P<0.05$) and fewer miscarriages (1 *vs.* 5; $P<0.05$). Confounding factors such as LMWH use for outcome was also investigated. Even if we demonstrated a trend towards a better outcome using LMWH for pregnancies prior PEG-IFN (live birth 2/3 on LMWH; miscarriage 1/5 on LMWH; $P=0.464$) or for all pregnancies (live birth: 8/12 on LMWH; miscarriage 2/6 on LMWH; $P=0.321$) it did not reach significance. The principal patients' characteristics and outcomes are summarized in Table 1.

This observational study (including 10 pregnancies in 8 ET patients) is the first case series of pregnant women treated with PEG-IFN evaluating pregnancy outcome, tolerance and safety. Here the rate of fetal loss (10%) is less than previously reported in retrospective cohort studies (34.5%-39.7%) and is in accordance with the reported outcomes of women treated with IFN during pregnancy.[8] Moreover we did not report any maternal, fetal complications or malformations. In terms of hematologic efficacy, platelet counts were well controlled with PEG-IFN, during pregnancy. PEG-IFN was relatively well tolerated and only a few grade 1-2 AEs were reported. No women experienced grade 3-4 side-effects or discontinued PEG-IFN due to toxicity. In past studies, standard IFN was shown to control platelet count in ET patients but was associated with significant and frequent side-effects causing drug discontinuation in up to 66%.[14] Moreover, because of its short half-life, patients usually required several subcutaneous injections per week. The efficacy of PEG-IFN in controlling the platelet count is similar to IFN, but its longer half-life allows less frequent injections and its tolerance profile results in less drug withdrawal.[15-17] The main limitation of our study was the small number of pregnancies reported; a key strength was that the management of these pregnancies is homogeneous and in accordance with modern obstetric and hematology practice, and more likely to reflect real time outcome data.

In addition, we cannot exclude the possibility that other confounding factors (e.g. LMWH use), in addition to PEG-IFN, contribute to the improvement in pregnancy outcomes. Although it would be naïve to suggest these data fully confirm the safety and efficacy of PEG-IFN, these provisional results do support ongoing use of PEG-IFN in the absence of evidence of harm and provide an alternative better tolerated treatment. Case ascertainment was based upon the physician's willingness to participate, and inclusion bias cannot be excluded. However, to avoid this bias, we requested that contributing hematologists included all pregnancies in women with a diagnosis of ET who received PEG-IFN, regardless of efficacy, complications or side-effects.

Current guidelines recommend using IFN as first-line for high-risk pregnant patients.[4] Our results highlight efficacy, safety and good tolerance of PEG-IFN, which could be an effective and safe alternative to IFN for pregnant woman with ET requiring cytoreduction.

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