Acquired Factor VIII Inhibitors In The Post-Partum Period

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BACKGROUND

Acquired Haemophilia A is a potentially life-threatening bleeding disorder due to the formation of polyclonal IgG_1 and IgG_4 autoantibodies directed towards Factor VIII. It is a very rare disorder with an incidence of 0.2-1.0 per million per year, of which 7-21% are associated with pregnancy. These women usually present with unexplained per vaginal bleeding or mucocutaneous bleeding within the first 4 months post-partum.
The diagnosis is based on a non-correcting prolongation of the APTT due to a Factor VIII inhibitor impeding Factor VIII activity and is confirmed with the Bethesda (-Nijemegen) assay. Pregnancy-associated Factor VIII inhibitors have a high rate of spontaneous eradication , with approximately 60% achieving remission within 30 months. However, immunosuppressants such as prednisone, cyclophosphamide or the anti-CD 20 monoclonal antibody, Rituximab can be used to accelerate this process .

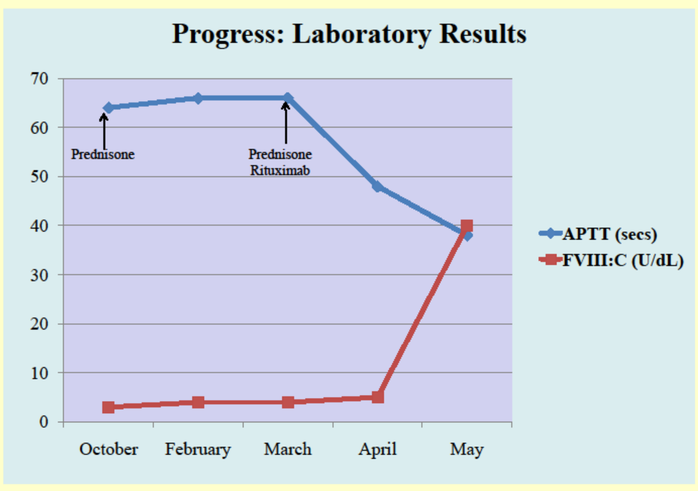
Achieving haemostasis in women with a bleeding phenotype secondary to pregnancy-associated Haemophilia A is paramount . Current recommendations suggest first-line use of "bypass agents" such as recombinant activated Factor VII (rFVIIa; NovoSeven®) and/or activated prothrombin complex concentrates (Factor VIII Inhibitor Bypassing Activity; FEIBA®) for superior haemostatic efficacy. However, these agents have an inherent risk of thromboembolism so their use during the high-risk post-partum period needs careful consideration.

We present two case reports of acquired Factor VIII inhibitors in the post-partum period that were successfully and safely managed with the bypass agent FEIBA®, without thromboembolic complications, together with accelerated inhibitor eradication with prednisone and Rituximab.

CASE STUDY 1:

Patient: Mrs LC 32 year old Caucasian woman
Obstetric History: G3P2 with an uncomplicated pregnancy, elective lower segment caesarian section delivery with no post-operative complications
Initial Presentation: Mucocutaneous bleeding with widespread ecchymoses and menorrhagia several weeks post-partum
Past Medical History: Chronic fatigue syndrome, Mood disorder with depression/anxiety and Irritable bowel syndrome
No clinical manifestation of autoimmune disease; ANA titre1:640
Laboratory Results:

	Diagnosis	Peak	At Eradication
APTT (25-37 sec)	64	66	-
FVIII:C (70-220 U/dL)	3	4	40
FVIII Inhibitor Titre (BU)	5.0	11.4	<0.5
Time to VIII Inhibitor Titre Peak (days)	-	116	-
Time to FVIII Inhibitor Titre Eradication (days)	-	-	199

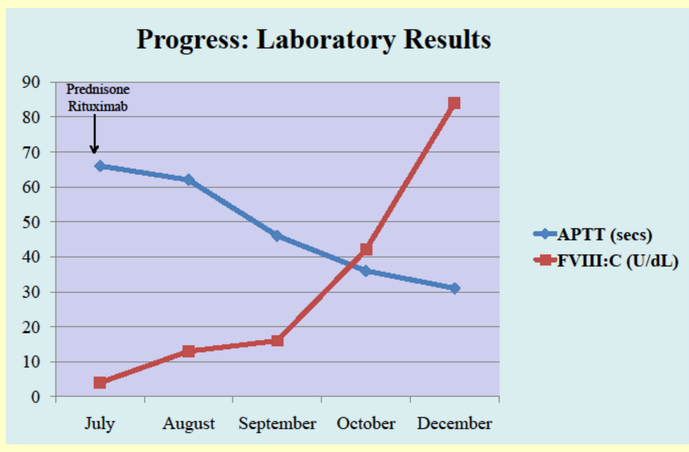


Initial Treatment: Haemostasis was rapidly achieved with FEIBA® at 50IU/kg q12hr, then used as required together with a tapering course of prednisone at 1mg/kg for inhibitor eradication.
Clinical Progress: Persistent presence of the FVIII inhibitor (after almost one year) together with clinical deterioration including the development of recurrent, spontaneous haemarthroses
Second-line therapy: FEIBA® at 50IU/kg used as required for haemostasis with a repeat tapering course of prednisone 1mg/kg with the addition of Rituximab at 375 mg/m^2 weekly for 4 weeks to accelerate inhibitor eradication without exposure to cytotoxic agents.
Outcome: Excellent haemostasis was achieved with FEIBA®; no thromboembolic complications occurred during the acute, high-risk post-partum period or during maintenance despite prolonged FEIBA® exposure. Furthermore, rapid inhibitor eradication occurred following the addition of Rituximab to prednisone.

CASE STUDY 2:

Patient: Mrs KS 36 year old Caucasian woman
Obstetric History: G2P1 with an uncomplicated pregnancy, emergency lower segment caesarian section after failed trial of forceps with immediate and life-threatening complications
Initial Presentation: Catastrophic primary and secondary post-partum haemorrhage resulting in an emergency laparotomy to evacuate a 16x16x5cm pelvic haematoma followed by a life-saving total abdominal hysterectomy
Past Medical History: Hashimoto's thyroiditis and Seronegative arthritis requiring prednisone during the second trimester
Laboratory Results:

	Diagnosis	Peak	At Eradiation
APTT (25-37 sec)	66	66	31
FVIII:C (70-220 U/dL)	4	4	84
FVIII Inhibitor Peak (BU)	3.1	3.1	<0.5
Time to FVIII Inhibitor Titre Peak (days)	-	0	-
Time to FVIII Inhibitor Titre Eradication (days)	-	-	137



Initial Treatment: Massive blood-product transfusion support, recombinant FVIII concentrate at 2000IU together with NovoSeven® at 90 mcg/kg q2hrs in an attempt to achieve haemostasis prior to transfer to a Haemophilia treatment centre
Subsequent Treatment: With inadequate haemostatic control, NovoSeven® was changed to FEIBA® at 50IU/kg q12hr together with tranexamic acid 1g q6hr with substantial clinical improvement. Given the severe bleeding phenotype the immediate use of Rituximab 375mg/m^2 weekly for 4 weeks together with prednisone at 1mg/kg was used to accelerate inhibitor eradication.
Outcome: Adequate haemostasis (persistent minor per vaginal bleeding) required regular FEIBA® and tranexamic acid; no thromboembolic complications occurred despite the very high-risk associated with the post-partum period, multiple abdominal/ pelvic surgeries or the prolonged use of FEIBA® together with an anti-fibrinolytic agent.

REFERENCES:

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WFH2014 5--P-W
Acquired Hemophilia
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DOI: 10.3252/pso.eu.WFH2014.2014
Poster presented at: WFH 2014 World Congress
PosterSessionOnline.com