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Analgesia, anaesthesia and obstetric outcome in women with inherited bleeding disorders

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ABSTRACT

Objective: Vertebral canal haematoma (VCH) complicates 1 in 168,000 obstetric epidurals (Ruppen et al., 2006). This risk is increased in women with inherited bleeding disorders (IBD). The impact of a contraindication to regional anaesthesia on pain management and obstetric outcome in these women is unknown. The purpose of this study was to determine anaesthetic use and obstetric outcomes in a cohort of women with IBD.

Study design: 97 women with IBD that delivered 130 babies at the CWIUH from Jan 2011 to Dec 2016 were identified from a maternal medicine database. Multidisciplinary planning of peripartum care was communicated to labour ward staff using a simple checklist. The primary bleeding disorders were: Von Willebrands disease (VWD) Type 1 27 (27.8%); VWD Type 2A 3 (3.8%); Low VWF 3 (3.8%); Bleeding disorder of unknown aetiology (BDUA) 19 (19.6%); deficiency of Factors VII, VIII, IX, X, and XI 13 (13.4%); Carriers of Factor VIII, IX, X, XIII deficiency 17 (17.5%); 5 had combined deficiencies (5.2%) and there was one platelet function defect. 9 had a family history of a bleeding disorder (9.3%). Haemostatic support, analgesia, mode of delivery and maternal and fetal outcomes were compared between pregnancies where regional anaesthesia was permitted and those that were not using the Chi-squared test.

Results: When pregnancies where regional anaesthesia was not recommended (49) were compared with pregnancies where regional anaesthesia was considered safe (81), the women were more likely to see an anaesthetist before labour 46 (94%) vs 46 (61%): $p < 0.001$; to require prophylactic haemostatic support for delivery 30 (61%) vs 1 (1%): $p < 0.001$; to use a remifentanil infusion 15 (31%) vs 0: $p < 0.001$, and have general anaesthesia for Caesarean Section (CS) 10 (20%) vs 1(1%): $p < 0.001$. Vaginal birth 35 (71%) vs 53 (65%): $p = 0.4$ and CS rates 14 (29%) vs 26 (32%) $p = 0.28$ were similar. Postpartum haemorrhage (PPH) was more common 11 (24%) vs 9(12%) vs $p = 0.07$ but not statistically so. There were no cases of neonatal bleeding or VCH.

Conclusion: Contraindication to neuraxial blockade in labouring women with IBD does not influence mode of delivery. This information is reassuring to these women who may be anxious about delivery without regional anaesthesia.

Introduction

Haemorrhage is a recognised complication of pregnancy and childbirth contributing to severe maternal morbidity and mortality worldwide [2]. The risk is increased in women who have inherited bleeding disorders (IBD). Physiological changes in pregnancy promote coagulation and clotting factors VIII and Von Willebrand Factor (VWF) increase as pregnancy advances [3]. The clotting deficiency in Von Willebrands Disease (VWD) (particularly Type 1) is corrected by pregnancy in most cases [4]. Factor VIII levels increase in Haemophilia A carriers [4] but Factor IX levels do not increase in Haemophilia B carriers [5] over the course of pregnancy. If an IBD does not correct during pregnancy, the woman is at increased risk of bleeding, especially peripartum. In this instance, prophylactic haemostatic support can be administered in the form of tranexamic acid, desmopressin (DDAVP), or the

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replacement of specific factors. There are no studies of adequate size to validate the safety and efficacy of these treatments in the prevention of postpartum haemorrhage in women with IBD. Some women have a significant bleeding phenotype but a specific haemostatic defect has not been identified i.e. they have a bleeding disorder of unknown aetiology (BDUA). The impact of pregnancy on their risk of bleeding is unknown, and haemostatic support may be warranted peripartum.

Central neuraxial blockades, namely epidural and spinal anaesthesia, are key components of pain management in labour. Vertebral canal haematoma (VCH) is a rare but serious complication that can result in neurological injury. In a review of 27 studies of 1.37 million women, the incidence of VCH was one in 168,000 of obstetric epidurals sited [1]. This risk is theoretically increased in women with IBD, but, good quality controlled studies to define this risk do not exist because these conditions are rare. For women with von Willebrands disease or with Factor VIII or IX deficiencies, current guidance recommends that neuraxial blockade may proceed once factor levels are > 0.5 IU/mL, but the evidence for this is sparse [6]. In the rarer factor deficiencies, there is even less evidence and care plans must be individualised with a multidisciplinary team. Spinal and epidural anaesthesia are not recommended in labour when an identifiable clotting deficiency has not corrected in pregnancy, or a woman has a diagnosis of BDUA.

Alternative methods for pain management include water immersion, hypnobirthing, TENS, and pharmacological options such as inhaled nitrous oxide, intramuscular and/or intravenous opioid. The biggest impact of a contraindication to regional anaesthesia is that CS has to be performed under general anaesthetic. The risks include failure to intubate and aspiration, and these complications are more frequent in pregnancy. In the confidential enquiry into maternal deaths in the UK, deaths attributed to anaesthesia have declined dramatically over the years. In the 2014 report there were two deaths from general anaesthesia in pregnancy [7]. This reflects the increased use of neuraxial blockade and decline in the use of general anaesthesia for labour and delivery.

The impact of a contraindication to regional anaesthesia on pain management and obstetric outcome in women with IBD is unknown. The purpose of this study was to determine the anaesthetic use in labour in a cohort of women with IBD and to determine if a contraindication to regional anaesthesia influenced obstetric outcome.

Materials and methods

Women with IBD that attended the maternal medicine service at our hospital, and delivered between January 1st 2014 and December 31st 2016 were identified from the clinic database. Most of the women had an IBD that was diagnosed prior to pregnancy and were registered on a national database. All women who attend the hospital are asked about personal and family history of bleeding disorders at booking. All patients with IBDs have baseline levels checked, where appropriate. Occasionally, where assessment occurs in pregnancy (e.g. family history and women not previously screened), a baseline non-pregnant level is not available. The diagnosis of BDUA was determined only after assessment in a specialised thrombosis service. Women who demonstrated a significant personal bleeding history as identified by the use of a physician directed standardised bleeding assessment tool and where full haemostatic investigations failed to identify a cause, were classified as having a BDUA. Haemostatic investigations include fibrinogen, vWF screen, factor levels II, V, VII, VIII, IX, X, XI and XIII, platelet aggregation studies and platelet nucleotide analysis.

Charts were reviewed and anaesthetic and obstetric data collected. Indicators of quality of care included haematology and an anaesthetic review prior to delivery; appropriate documentation of MDT recommendations and administration of haemostatic support and regional anaesthesia. Products available for haemostatic support included tranexamic acid, DDAVP, specific coagulation factor concentrates where appropriate, and plasma and platelet transfusion where appropriate. All women requiring haemostatic support have a plan in place, and this is communicated using the care plan for delivery. The plans are developed by a haematologist, in conjunction with the MDT, and follow international [8] and national guidelines [9,10] where available.

The majority of these women were cared for by a specialized maternal medicine team consisting of obstetricians, haematologist, anaesthetists and a specialized midwife from antenatal booking to six weeks post delivery. A care plan for labour and delivery was completed after multidisciplinary discussion and inserted in the woman's records. This plan was based on serial blood factor level measurements (where appropriate) and recommendations for haemostatic support and safety of regional anaesthesia were made in keeping with international best practice. [8,11–13]. Analgesia, anaesthetic and obstetric outcomes were compared in pregnancies where regional anaesthesia was not recommended and pregnancies where regional anaesthesia was considered safe using the chi-squared test ; $p < 0.05$ was considered to be statistically significant. The study was approved by the hospital research and ethics committee.

Results

97 women were identified, with a total number of 130 labour and deliveries. The bleeding disorders are outlined in Table 1. The main diagnosis was VWD Type 1 (27) 27.8%, (one severe i.e. VWF < 0.1 IU/ml and a combined factor deficiency in two). There were 3 cases of VWD Type 2A and two were carriers of severe Factor VIII deficiency. 19 women (19.6%) had BDUA. 13 had deficiencies of FVII, VIII, IX, X, and XI. 17 were carriers of Factor FVIII, IX, X, or XIII deficiency. 5 women had combined deficiencies and one had platelet function defect. 46.4% had significant personal bleeding histories with menorrhagia, easy bruising, nosebleeds, excessive surgical bleeding or postpartum haemorrhage. 52 (53.6%) had a family history of a bleeding disorder. 46 (35%) were first time births.

Indicators of quality of care are shown in Table 2. All women had a haematology and 92 (74%) had an anaesthetist consultation prior to delivery. When prophylactic haemostatic support was indicated peripartum, it was recorded clearly in the chart and given in all but three cases, where delivery occurred rapidly before tranexamic acid could be administered. Regional anaesthesia was considered to be unsafe in 49 (38%) and one woman in this group had neuraxial blockade in error. She was transferred from another hospital and haematology review was requested because of a strong family and personal history of bleeding. Preliminary

Table 1
Primary diagnosis in each patient.

	N:	%:
Von Willebrand Disease Type 1	27	27.8
Von Willebrand Disease Type 2A	3	3.1
Low VWF	3	3.1
Deficiencies of Factors VII, VIII, IX, X, XI	13	13.4
Carriers Factor VIII, IX, X, XIII	17	17.5
Combined deficiencies	5	5.2
BDUA	19	19.6
Platelet function defect	1	1.0
FHx of Bleeding disorder/BDUA only	9	9.3

Table 2
Intervention for each birth.

	N:	%:
Antenatal Haematology review	130	100
Antenatal Anaesthetic review	92	74
Haemostatic support required	34	26
Haemostatic support given appropriately	31/34	91
Regional Anaesthesia considered unsafe	49	38
Regional Anaesthesia administered	1/49	2

investigations led to a provisional diagnosis of BDUA with platelet function tests planned. A letter outlining her potential diagnosis and planned investigations was in her chart, but not a peripartum care plan, and there was no recommendation made regarding the safety of regional anaesthesia. She went into preterm labour with a breech presentation and had an emergency CS under spinal anaesthesia. One woman with FIX deficiency was advised against neuraxial anaesthesia but this decision was reversed following MDT discussion on the day of delivery. FIX levels were corrected before induction of labour and, it was decided that it would be safe for her to have an epidural. She subsequently required a CS and this was performed following epidural top up.

When pregnancies with a contraindication to regional anaesthesia are compared to those for whom it is safe, the women are similar in age and parity (Table 3), but are more likely to have low factor levels in the third trimester and require haemostatic support for delivery. The use of non- pharmacological analgesia, nitrous oxide and pethidine is similar in both groups. One woman in the contraindicated group had neuraxial blockade as discussed above. One third of the group that could not have an epidural used remifentanil for analgesia and ten women had a general anaesthetic for CS. One patient in the group that was allowed regional anaesthesia had a general anaesthetic because the epidural provided inadequate pain relief for CS.

The rate of induction was higher when regional anaesthesia was contraindicated 18 (37%) vs 25 (31%) but not statistically so ($p = 0.25$). The rate of CS 14 (29%) vs 26 (32%); $p = 0.28$, and vaginal delivery 35 (71%) vs 53 (65%); $p = 0.4$ was similar in both groups. Primary PPH was higher in the group where neuraxial blockade was not recommended 11(24%) vs 9 (12%) but this did not reach statistical significance (Table 3). There were no anaesthetic complications and no neonatal haemorrhage.

Table 3
Clinical Characteristics.

	Regional allowed	No regional	p-value
Clinical Characteristics			
Number	81	48	
Parity	1(0–6)	1(0–5)	0.87
Low 3rd Trimester levels	0	17	<0.001
Antenatal anaesthetic review	46(61%)	46(94%)	<0.001
Haemostatic support required	1	30	<0.001
Anaesthesia			
Non pharmacological	10(13%)	5(10%)	0.33
Inhaled Nitrous Oxide	39(50%)	29(59%)	0.31
Pethidine IM	2(3%)	2(4%)	0.63
Epidural	34(44%)	0	<0.001
Remifentanil	0	15(31%)	<0.001
Spinal for CS	18(23%)	1(2%)	<0.001
General Anaesthetic for CS	1(1%)	10(20%)	<0.001
Labour			
Onset of Labour			
Spontaneous	40(51%)	20(41%)	0.28
Induction	25(31%)	18(37%)	0.25
CS-Elective	11(14%)	10(20%)	0.38
Mode of Delivery			
Vaginal	53(65%)	35(71%)	0.4
CS-Emergency NIEL	6(8%)	1(2%)	0.19
Emergency in Labour	9(12%)	3(6%)	0.33
PPH	9(12%)	11(24%)	0.07

Comment

The incidence of IBD in the general population ranges from VWD (1%) [14] to the rarer Haemophilia A (FVIII deficiency, 1/5,000 male births) and Haemophilia B (FIX deficiency, 1 in 30,000 male births) [15]. More than half of haemophilia cases are severe (i.e. factor activity <0.01 IU/mL). Female carriers of this X-linked condition rarely have severe disease but up to one quarter of female carriers may have coagulation factor levels <0.40 IU/mL, consistent with mild haemophilia. A further group of women with a bleeding phenotype but no defect in haemostasis on traditional testing are known to have a "bleeding disorder of unknown aetiology" (BDUA). The uncertainty as to the pathogenic mechanism for bleeding in this cohort makes counselling regarding risk particularly challenging.

This study provides information about anaesthetic and obstetric outcomes in a large cohort of women with IBD, when haematological, anaesthetic and maternity care is delivered by a specialized team. An individualised care plan is placed in each patients chart and is designed to simplify peripartum care for the labour ward or theatre teams who may not have experience in looking after women with these disorders. The quality of care indicators are reassuring. All of the women were seen by a haematologist, on average in the second trimester of pregnancy.

Two thirds of the women were seen by an anaesthetist in the antenatal period and all, but one, of the women that were advised against regional anaesthesia were seen and a care plan for analgesia placed in the chart. Haemostatic support was indicated peripartum in approximately one quarter of women and, in most cases; this was achieved by the administration of Tranexamic acid. DDAVP was used in one woman and factor replacement therapy in three. The unpredictable nature of obstetrics is evident from the three women who presented in advanced labour and delivered before tranexamic acid could be administered. One woman received regional anaesthesia in labour when contraindicated. This represents a communication failure and highlights the importance of MDT discussion and access to a clear peripartum care plan in the patients' notes. Reversal of the care plan evidenced by the case of FIX deficiency is an excellent example of how plans can fluctuate based on a risk benefit analysis in labour with MDT discussion. This woman was spared the risk of general anaesthesia for her delivery.

When pregnancies where regional anaesthesia was not recommended were compared with pregnancies where regional anaesthesia was considered safe, maternal age and parity were similar. Factor levels were lower and they were more likely to require haemostatic support in labour. Inhaled nitrous oxide was used in 59% of the study group and 4% used intramuscular pethidine. Parenteral opioids are easy to administer, low cost and not invasive but a recent systematic review showed that up to two thirds of women had moderate or severe pain and /or poor or moderate pain relief even when used intravenously or with PCA [16]. They are also associated with drowsiness, nausea and vomiting. Remifentanil is an ultra-short acting opioid that is patient controlled with a built in 'lock out' period to avoid overdose. Respiratory depression can occur, however, and monitoring of pulse oximetry and respiratory rate with 'one to one' midwifery care is advisable. When regional anaesthesia was contraindicated in labour, one third of women required remifentanil. We do not have data to assess patient satisfaction with this mode of analgesia but the analgesic effect in labour is good in published studies but not as effective as an epidural [17].

General anaesthesia poses a greater risk to the pregnant woman. Weight gain, increased breast size and left lateral tilt can make positioning of the head and neck suboptimal. The diameter of the oropharynx reduces as pregnancy advances, most likely because of fluid retention and tissue oedema [18]. An increased risk of gastric aspiration results from reduced tone of the gastro-oesophageal sphincter and increased intrabdominal pressure. Oxygen consumption is increased, functional residual capacity is reduced and hypoxemia develops more quickly. Twelve women had general anaesthesia for CS. The majority were elective procedures and for obstetrical reasons e.g. previous CS (3), malpresentation (1), multiple pregnancy (1), and previous myomectomy (1). In the group that were permitted neuraxial blockade, there was one woman who required general anaesthesia because the regional technique did not provide adequate anaesthesia for CS. In the group where neuraxial blockade was contraindicated, there were two emergency CS and there was no Category 1 CS in either group. 74 neuraxial techniques performed without complication in 72 women with VWD in labour were identified in a 2009 systematic review. 10 cases required desmopressin, VWF and or FVIII concentrate and the remaining cases had normal VWF levels at delivery [6]. The women with VWD in our study contribute to the data regarding safety of neuraxial blockade when VWF levels are greater than 0.5 IU/ml.

Induction of labour was similar whether or not regional anaesthesia was recommended. Induction may be considered preferable to spontaneous labour to facilitate the administration of haemostatic support and availability of experienced staff at the time of delivery. Elective CS was mainly performed for obstetric reasons. It is encouraging to note that there is an excellent chance of achieving vaginal delivery when vaginal birth is planned. These figures are not different from the 8632 women who delivered at our hospital in 2014 [19] where the rate of induction of labour was 31%, vaginal delivery was 72% and CS was 29%.

Primary PPH was higher in pregnancies where neuraxial blockade was not advised (24 vs 12%) but is in keeping with the range of 0–48% reported in women with IBDs [20]. This occurred despite correction of factor levels (where possible) and active management of the third stage of labour. In VWD, the commonest IBD in our group, it is unclear what level of VWF should trigger desmopressin or prophylactic recombinant VWF replacement. Expert groups recommend the VWF levels be maintained greater than 0.50 IU/mL [11] and yet VWF is normally elevated greater than 1.0 IU/mL because of the normal physiology of pregnancy. It may be that a higher threshold is required and for a longer period of time and that is why higher rates of PPH (both primary and secondary) are reported [21,22]. The difference in primary PPH did not reach statistical significance in this study but the numbers are small. Of note the background rate of primary PPH reported for the entire hospital population in 2014 was 9.1% [19]. There was no case of neonatal haemorrhage.

Limitations of the study are that the numbers are small and include a broad spectrum of different IBDs. It is difficult, however, to accrue large numbers because of the rarity of some of these conditions. The model of care is unique, however, and the data has been extracted from medical charts.

Summary and conclusions

The spectrum of IBDs that may present for antenatal care is shown in this study. These women should attend a specialised multidisciplinary team and have an individualised care plan that can be followed with ease by labour ward staff and theatre staff when she has her baby. Women are anxious about analgesia and anaesthesia in labour [23] and understandably, more so, when they are aware that they are unable to have an epidural or spinal. This study shows what alternative analgesia is used in labour and, reassuringly, that labour outcome is the same.

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