Thrombosis Research (2007) **120**, 387–390

THROMBOSIS RESEARCH

intl.elsevierhealth.com/journals/thre

BRIEF COMMUNICATION

Evaluation of the clinical safety of desmopressin during pregnancy in women with a low plasmatic von Willebrand factor level and bleeding history

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Received 12 May 2006; received in revised form 12 May 2006; accepted 12 September 2006
Available online 20 October 2006

KEYWORDS
von Willebrand factor;
Women;
Pregnancy;
Desmopressin

Introduction

The diagnosis of von Willebrand disease (VWD) is rather difficult, considering the biologic heterogeneity especially in type 1, the most frequent type of the disease. Two surveys in developing countries indicate that VWD is under-diagnosed and untreated, because, in part, the diagnostic capabilities are limited. Most forms of VWD respond to desmopressin (DDAVP), which is easily obtainable and affordable in many developing countries [1], and is the optimal alternative treatment because it does not transmit blood-born diseases.

Although previous work [2] has not been able to define a reliable marker of bleeding risk, some symptoms can predict bleeding complications. Several patients, especially women, express bleeding tendency only under challenges such as childbirth, menses, and after teeth extraction or surgery [2,3]. Higher incidence of primary and secondary post-partum hemorrhage in women with VWD has been documented [4–7]. Bleeding is more likely when FVIII is lower than 50 IU/dL in the 7th or 8th month of pregnancy [6]. However, the literature is scanty about the use of desmopressin in pregnant women [8,9].

Considering the previous bleeding events we reviewed the antenatal use of DDAVP in 54 women from our Department, with focus on mother and newborns outcomes.

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0049-3848/$ - see front matter
doi:10.1016/j.thromres.2006.09.004

Patients and methods

Patients

We performed a retrospective cohort study from 1990–2005 in our Department. The study was approved by the Institutional Review Board. The records of women with von Willebrand factor (VWF) levels lower than 50 IU/dL (ratio ristocetin cofactor/von Willebrand antigen>0.7) and bleeding symptoms that had completed a pregnancy within 1990–2005 were reviewed to identify those women that had used DDAVP related to pregnancy or childbirth (dose in all cases 0.3 μg/kg pre-pregnancy weight). Demographic data, details of the obstetric history, and information about gynecological and surgical history, with quantification of menstrual blood loss using the Pictorial Bleeding Assessment Chart scoring method [10] were recorded. Bleeding was defined as major if it was clinically overt and associated with either a decrease in the hemoglobin level of at least 2 g/dL or the need for transfusion of 2 or more units of red cells.

Blood samples and laboratory assays

FVIII:C was assayed by the one-stage method using Factor VIII deficient plasma (Biopool, Ventura, USA). von Willebrand factor antigen (VWF:Ag) was measured by a home-made sandwich enzyme linked immunosorbent assay (ELISA) which uses biotinylated rabbit anti-human VWF (DakoCytomation, Glostrup, Denmark) and avidin/biotinylated peroxidase complex for its detection. von Willebrand factor activity (VWF:RCo) was measured by an aggregometric method using formaline-fixed platelets and ristocetin (ABP, New Jersey, USA). All assays were calibrated against a pooled normal plasma, using the International Reference Preparation for Factor VIII:C Related Activities in Plasma (IRP) (87/718, National Institute for Biological Standards and Control, UK) as reference plasma.

DDAVP test and criteria for biologic response

Prior to pregnancy, 34 patients had undergone desmopressin test-infusion to assess biological responsiveness and its possible clinical usefulness. Intravenous infusion of 0.3 μg/kg body weight DDAVP (diluted in 50 mL saline) over 20 min was given under medical supervision, without receiving contraceptive or hormonal treatment. Venous blood was withdrawn at baseline and 1, 2 and 24 h after the infusion ended. Aliquots of platelet poor plasma samples were obtained and frozen at −70 °C until tested (VWF:Ag, VWF:RCo). The advice of fluid restriction, in the first day after infusion, was given to all patients. Responsive women were defined as those who, 1 and 2 h after the end of DDAVP infusion, had an increase of plasma FVIII:C, VWF:Ag and VWF:RCo of at least 3-fold over baseline and reached levels of at least 50 IU/dL for all values.

Results

The use of DDAVP during pregnancy and delivery was evaluated in 54 women with a low plasmatic level of VWF and bleeding tendency, with special concern on its safety for mother and child. The characteristics of women and their bleeding symptoms are delineated in Table 1. Ten out of the 54 women (20.4%) had presented 11 major bleeding episodes previous to the diagnosis of VWD: 5 post-partum (4 vaginal deliveries/1 cesarean section), 2 post-surgery (tonsillectomy, inguinal hernia repair), and 1 epistaxis, post-tooth extraction, menorrhage and miscarriage each one.

The mean levels and ranges of FVIII:C, VWF:Ag and VWF:RCo in the non-pregnant state are described in Table 2. Three women had VWF levels between 10 and 20%, 7 had levels between 21 and 30%, and 44 women had levels between 31 and 49%. The DDAVP test, performed before pregnancy, was available in 34/54 (63%) women; all with good response. Factor levels were checked at 7th–8th month of pregnancy and the results are delineated in Table 2.

DDAVP was administered in the first trimester of 5 pregnancies in 3 women. One of them presented vaginal bleeding in the first trimester with an ultrasonographic diagnosis of retroplacental haematoma and a viable fetus that was treated with bed-rest and progesterone. When the haematoma increased, DDAVP was indicated for two consecutive days, with haematoma resolution by ultrasonography. Four cervical cerclages in 2 women were performed between 10 and 12 weeks with DDAVP prophylaxis. Neither water overload nor increase in uterine tone was observed. Newborns exposed to DDAVP in the first trimester were healthy.

DDAVP was administered as a single dose in intravenous infusion in 30 vaginal deliveries and 45 cesarean deliveries. In all cases the cesarean section was indicated because of obstetric causes.

Table 1 Patients characteristics

Patients characteristics	
Age (years, mean and range)	28.6, 18–42
Bleeding symptoms	
Nose–gum bleeding/easy bruising	55.5%
Menorrhage	53.7%
Post-partum bleeding history	38.7%
Post-surgery	27.8%

Table 2 Mean levels and ranges of factor VIII, von Willebrand antigen and ristocetin cofactor in the non-pregnant state and during the 7th–8th month of pregnancy

Timing of study	Factor VIII %, (range)	von Willebrand antigen %, (range)	Ristocetin cofactor %, (range)
Non-pregnant state	51 (12–95)	41 (20–50)	41 (20–49)
7th–8th month of pregnancy	84 (35–160)	120 (49–180)	89 (49–146)

Desmopressin was indicated in 35 women (27 vaginal deliveries and 25 cesarean sections) because the laboratory parameters at 7th–8th month of pregnancy showed abnormalities. Sixteen women received DDAVP prophylaxis because a cesarean section was decided ($n=20$); finally, in 3 women with vaginal delivery the indication was performed in the operating room by the obstetrician and/or the anesthesiologist.

In 53 deliveries, the DDAVP was infused before the anesthesia (5/53 general anesthesia and 48/53 epidural blockade). Local complications associated with the epidural placement were not observed. Twenty-two vaginal deliveries were performed without anesthesia, and DDAVP was infused at the onset of labor.

The weight of newborns was available in 63/75 childbirths: mean was 3.3 kg (range 2.2–4.5). No baby was premature, and neonatal bleeding was not reported. There was no hyponatremia in mothers, and none of the patients presented thromboembolic complications. A second dose of DDAVP was not required.

Discussion

In this retrospective study, the pregnancy outcome of VWD women from a single institution, which were treated with DDAVP, was analyzed. There have been several concerns regarding the use of DDAVP antepartum: the chance of maternal and neonatal hyponatremia, and the oxytocin-like effects on uterine muscle [11]. Hyponatremia and volume overload, due to the antidiuretic effect of desmopressin, are relatively rare if fluid intake is not excessive during treatment [12]. DDAVP has little or no oxytocic activity or vasopressor effect [13], and it could be safe during the pregnancy as it has been reviewed by different authors [8,14–16].

FVIII and VWF activities increase progressively during normal pregnancy [17]. Most women with type 1 VWD have an increase in FVIII and VWF levels into the normal non-pregnant range [6], therefore the women with VWD mostly do not bleed during pregnancy [3]. However, the individual haemostatic response to pregnancy is variable and the childbirth carries a higher risk of post-partum bleeding in several patients [6]. Mannucci [9] referred his experience about the use of DDAVP in the first trimester of pregnancy in 31 women with low FVIII levels, only 5 VWD type 1 patients, to prevent bleeding at the time of chorionic villus sampling and amniocentesis without adverse effects.

In our report, at the end of the first trimester, between 10 and 12 weeks, three women received DDAVP for 5 procedures without adverse effects. Their newborns were in good health and appropriate weight. The mothers did not show any clinical complications.

We also prescribed DDAVP in 30 vaginal and 45 cesarean deliveries. In 48 cases, DDAVP was infused previous to the epidural catheter placement for analgesia without local complications. Although it is not our purpose to establish recommendations concerning lumbar punction in women with VWD, if FVIII/VWF did not reach haemostatic levels [6], we believe that VWD women could benefit from labor analgesia using DDAVP prophylaxis. Mannucci had suggested that in several cases it could be necessary to administer desmopressin or concentrates at the time of delivery and for three to four days thereafter [12]. However, Kouides mentioned that it is not clear whether intermittent DDAVP prophylaxis should be carried out for several weeks post-partum [16]. In our series, the effective haemostasis was obtained with a single dose of DDAVP at the time of delivery, avoiding fluid retention.

Although there are some reports of the antepartum and peripartum use of DDAVP in VWD without the development of harmful effects, no controlled trial has been conducted to evaluate the efficacy and safety for mothers and babies. Our study describes the use of DDAVP in pregnant patients with low VWF levels and history of bleeding tendency. DDAVP could be a safe therapy for prevention of post-partum bleeding.

In summary, we reviewed the records of 54 women with a low plasmatic VWF level and bleeding history, who had used desmopressin during pregnancy. No adverse effects were observed in mothers or newborns, including those exposed to the drug during the first trimester. No local complication of epidural placement was observed. DDAVP merits to be considered as the first choice of therapy [1], when patients with a previous or current low plasmatic VWF level present bleeding complications, including pregnant women. Although post-partum bleeding will appear in a small proportion of women with VWD, there is no accurate way to identify who is going to

bleed. The use of DDAVP should be regarded as a highly valuable option.

Acknowledgments

This study was supported by a research grant from Fundación René Barón, SECYT and Ministerio de Salud, Argentina. Arizó A has been awarded by a clinical fellowship "Adolfo H. Aztiria" from Academia Nacional de Medicina.

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