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REVIEW ARTICLE

von Willebrand disease and pregnancy

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Von Willebrand disease (VWD) is the most common inherited bleeding disorder, found in approximately 1% of the general population, without ethnic differences [1,2]. VWD is the result of a deficiency or defect in von Willebrand factor (VWF), the large multimeric protein which mediates platelet adhesion and serves as a carrier protein for factor VIII (FVIII). There are three major types. Type 1 is the result of a partial, quantitative deficiency of a structurally normal VWF, and accounts for 70–80% of all VWD patients. Type 2 (20% of VWD patients) includes several qualitative defects in VWF that affect its multimeric structure or function. Patients with type 3 VWD (5–10% of VWD patients) are homozygous or doubly heterozygous for two mutant VWF alleles, with a resulting complete deficiency of VWF and a secondary severe deficiency of FVIII. Although the autosomal inheritance pattern predicts that both sexes should be equally affected, there is a higher frequency of symptomatic VWD in women because of the hemostatic challenges of menses, pregnancy and delivery [3–5]. This review focuses on the bleeding complications experienced by women with VWD during pregnancy, and the efficacy and safety of available therapies.

Factor VIII and VWF levels during pregnancy

There is a progressive increase in FVIII and VWF levels during normal pregnancy [6]. Most studies suggest an increase beginning during the second trimester, with peak levels at term, followed by a return to baseline during the postpartum period [6–12]. FVIII and VWF levels also increase in most women with VWD, which may explain the frequent improvement in minor bleeding manifestations during pregnancy [13–15]. The hemostatic response to pregnancy depends on both the type and severity of disease. Most women with type 1 VWD have a progressive increase in FVIII and VWF levels into the normal non-pregnant range, which may mask the diagnosis during pregnancy [16,17]. However, levels may remain low in severe cases [14,16,18,19]. FVIII and VWF antigen levels often increase during pregnancy in women with type 2 VWD [14,16,18]. Most studies show minimal or no increase in VWF activity levels, and a persistently abnormal pattern of multimers, reflecting the increased production of an abnormal VWF [14,16,18,20]. However, a woman with undetectable VWF activity at baseline achieved a level of 100% at term, illustrating the variable individual hemostatic response [10]. Most women with type 3 VWD have no improvement in FVIII or VWF levels during pregnancy [13,21], although an increased FVIII level has been rarely reported [17].

Very few studies have measured FVIII and VWF levels during the postpartum period. The limited available evidence suggests marked inter-individual variability in the rate of decline of FVIII and VWF levels after delivery [8,9]. However, VWF levels may fall precipitously after delivery in women with VWD [10]. The changes in clotting factor levels during and after pregnancy are assumed to parallel fluctuations in hormone levels, although there are no studies showing a direct correlation. In one woman with type 2A VWD, VWF activity decreased dramatically from a peak level of 100% at term to approximately 10% of normal within the first 24 h postpartum. A similar rapid decline in estradiol to 10% of normal non-pregnant levels occurred during the same time period [10]. The postpartum fall in VWF explains the risk of postpartum hemorrhage, even in women with type 1 disease. The individual hemostatic response to pregnancy is variable, emphasizing the importance of monitoring VWF and FVIII levels in women with type 1 and 2 disease [8–10,13,17]. The increase in clotting factor levels is similar during consecutive pregnancies in most, but not all, cases [14,18].

Bleeding during pregnancy

Women with VWD are at risk from a variety of bleeding complications during pregnancy, as a result of invasive prenatal diagnostic and monitoring procedures, spontaneous or elective abortions, and the hemostatic challenge of delivery. There are no prospective studies defining the risk of bleeding in these settings; estimates are based on surveys and small case series.

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Antepartum bleeding

Since FVIII and VWF levels do not increase significantly until the second trimester, women with VWD remain at risk from bleeding in early pregnancy. In one series, first-trimester vaginal bleeding occurred in 33% of pregnancies [13]. Antepartum hemorrhage is uncommon but may occur after spontaneous miscarriage or elective termination, occasionally as the initial presentation of VWD [13,21,22]. In one study, 10% of spontaneous or elective abortions were complicated by excessive bleeding requiring transfusion. Intermittent bleeding 2 weeks after miscarriage occurred in 30% of cases [13]. In another series, 3.8% of women with VWD had bleeding at the time of abortion [4]. There are other case reports of hemorrhage during the first few weeks after pregnancy termination [22–25].

Postpartum hemorrhage

Multiple retrospective studies suggest that women with VWD are at increased risk for postpartum hemorrhage (Table 1). In a telephone survey of gynecological and reproductive health, 59% of women with VWD reported excessive postpartum bleeding, compared to 21% of unaffected controls [26]. An older Swedish series found a lower overall prevalence of 23% of women [4]. However, the frequency of postpartum hemorrhage was 34% when the analysis was limited to women who had been pregnant. Three other series included a total of 51 women, with information on 92 deliveries [13,14,18]. Primary postpartum hemorrhage (defined as > 500 ml blood loss in the first 24 h) complicated 16–29% of pregnancies, requiring blood transfusions in the majority of cases. Primary postpartum hemorrhage occurred more commonly in women with type 2 VWD variants, and in those with VWF levels < 50% of normal at term [14,18]. Secondary postpartum hemorrhage (after the first 24 h) complicated 20–29% deliveries and also frequently required blood transfusions [13,14,18]. Several women had recurrent episodes after subsequent pregnancies [13,14]. VWF levels at the time of hemorrhage were unknown in most women, but were < 50% in those who had postpartum testing. The diagnosis of VWD was unknown prior to presentation with postpartum hemorrhage in a substantial number of cases [27]. In the largest study, there was no postpartum hemorrhage in women who received prophylactic therapy [13]. However, postpartum hemorrhage has been reported in women who received VWF-containing concentrates or cryoprecipitate at delivery [14,18,25,28]. Intermittent postpartum bleeding may also persist for prolonged periods [13,14].

Table 1 Frequency of postpartum hemorrhage in women with von Willebrand disease

Haemorrhage type	% of all deliveries	% women with VWD	Reference
Primary*	16–29	23–43	
Secondary†	20–29	29–43	[4, 13, 14, 18]
Overall‡	38–50	34–71	
VWD Subtype§			
Type 1	10–37	16–42	[14, 22, 23, 31]
Type 2	50–54	18–83	[14, 22, 31]
Type 3	27	15–26	[22, 31, 33]

*More than 500 ml blood loss within first 24 h after delivery; †more than expected amount of blood loss more than 24 h after delivery until 6 weeks postpartum; ‡overall frequency of postpartum hemorrhage (primary or secondary); §frequency of postpartum hemorrhage in different subtypes of von Willebrand disease.

The frequency of postpartum hemorrhage in the different types of VWD is not well defined (Table 1). Postpartum hemorrhage was reported by 32% of women with type 1 VWD in surveys conducted by telephone or questionnaire [29,30]. Transfusions were required in 25% of cases and several women underwent a hysterectomy. Recurrent postpartum hemorrhage after subsequent pregnancies was reported by 80% of those with a first episode. In a large Italian registry of VWD patients, summarized in recent reviews, postpartum hemorrhage occurred in 17% and 18% of women with type 1 and 2 disease, respectively [31,32]. In small case series, postpartum hemorrhage complicated 10–37%, and 50–54% of deliveries in women with type 1 and type 2A disease, respectively [14,22,23]. Postpartum hemorrhage occurred in 15–26% of women with type 3 VWD, usually in the setting of suboptimal doses or duration of prophylactic therapy [22,31–33].

Interpretation of the data is limited by incomplete information about clotting factor levels, prophylactic therapy and other contributing causes. Smaller series and surveys relying on patient report found higher rates of hemorrhage [26,29] than larger series that included confirmatory details of obstetric history [13,14,18]. Selection bias is possible in studies of women using specialized treatment centers because these women may have more severe bleeding complications [13,18]. Nevertheless, the available evidence suggests that women with VWD are at substantial risk from postpartum hemorrhage because of the rapid fall in FVIII and VWF levels after delivery. The risk is higher in women with type 2 and type 3 disease, especially those with low FVIII and VWF levels (< 50%) at term who do not receive adequate prophylactic therapy. The risk persists for several weeks, with reports of hemorrhage up to 3–5 weeks postpartum [4,14,16]. VWD may also exacerbate bleeding due to other obstetric causes, such as uterine atony or a traumatic delivery. The prevalence of undiagnosed VWD in women with postpartum hemorrhage is unknown. One small series found no cases in 14 women with postpartum hemorrhage tested on a single occasion [34].

Epidural/spinal anesthesia

There are no studies defining guidelines for the use of regional anesthesia during labor and delivery in women with VWD. Anesthesiologists are often reluctant to administer epidural anesthesia because of the risk of a spinal hematoma causing spinal cord compression. There is no consensus on safe VWF and FVIII levels for placement of an epidural catheter. The

current evidence is limited to case reports of women with VWD who received epidural anesthesia without bleeding complications. Two women, one with type 2A and the other with type 3 disease, received prophylactic VWF containing concentrates, with VWF and FVIII levels > 100% prior to the procedure in both cases [21,35]. Another woman with a ristocetin cofactor activity of 10% at term (normal bleeding time and FVIII level) received epidural anesthesia without prophylactic therapy or bleeding complications [36]. There is also a report of uncomplicated epidural anesthesia in a woman with an FVIII level of 200% and a mildly prolonged bleeding time. Prophylactic therapy was not given prior to catheter placement, but she received desmospressin (DDAVP) before catheter removal [37]. In another series, eight women with VWD received regional anesthesia during labor and delivery without bleeding complications. Only one woman received prophylactic therapy but clotting factor levels were > 50% in the other cases [13]. The decision to use epidural anesthesia for delivery requires a careful risk–benefit assessment by the hematologist and anesthesiologist. Prompt catheter removal prior to the postpartum fall in clotting factor levels will reduce the risk of bleeding.

Other bleeding complications

Other pregnancy-associated bleeding reported in women with VWD includes extensive bruising and hematomas at intramuscular injection, episiotomy and surgical wound sites, which may require drainage in rare cases. Delayed acute bleeding from episiotomy wounds, severe enough to require transfusion, may also occur [13,18,21,38]. Most of these complications occurred in the absence of, or after discontinuation of, prophylactic therapy. There are no studies estimating the risk of bleeding associated with other invasive procedures such as amniocentesis, chorionic villus sampling, *in vitro* fertilization, or cervical cerclage. Although excessive bleeding has not been reported, prophylactic therapy is probably given to high-risk women.

Type 2 VWD

The diagnosis and management of several type 2 variants of VWD present special problems during pregnancy.

Type 2N VWD

Type 2N VWD is a result of mutations which selectively inactivate the binding site for FVIII on VWF. Although VWF-dependent platelet function is preserved, FVIII levels are low because of rapid clearance in the absence of binding to VWF. Affected patients have FVIII levels that are 5–40% of normal but have normal VWF levels and multimer pattern. Symptomatic patients are homozygous or compound heterozygous for type 2N mutations alone, or with a second VWF mutation preventing expression of the other allele [3,39]. Despite increased FVIII and VWF production during pregnancy, FVIII levels are often low because of impaired binding by the abnormal VWF. The increase in FVIII level during pregnancy and after therapy may depend on the specific mutation and on the severity of the resulting binding defect [40]. FVIII levels ranged from 6 to 42% at term in the few reported cases of pregnant women with type 2N VWD [41–43]. FVIII levels may fall precipitously after delivery, as in other types of VWD [41]. Women with persistently low FVIII levels are at risk for postpartum hemorrhage and may require prophylactic therapy for delivery [44]. DDAVP and immunopurified or recombinant FVIII products increase FVIII levels but with an often markedly attenuated duration of effect because of impaired stabilization by the variant VWF [42,45]. In contrast, VWF-containing FVIII concentrates maintain hemostatically effective FVIII levels for more prolonged periods, and provide effective prophylaxis in pregnant women with type 2N disease [42,43].

The diagnosis of type 2N VWD should be considered in women with low FVIII and normal VWF levels, especially in the absence of an X-linked pattern of inheritance. Diagnosis during pregnancy may be masked by an increase in FVIII levels to the normal range in milder cases. Affected women may be misdiagnosed as carriers of hemophilia. Accurate diagnosis is essential for genetic counseling and optimal therapy. FVIII-deficient male fetuses are at risk for serious bleeding complications at the time of delivery. In contrast, bleeding is unlikely in an obligate heterozygote offspring of a woman with a homozygous or double heterozygous type 2N mutation.

Type 2B VWD

Type 2B VWD results from 'gain of function' mutations producing a variant VWF with abnormally increased affinity for the platelet GPIb receptor. Spontaneous binding of VWF to platelet GPIb results in clearance of the high-molecular-weight multimers, and often mild thrombocytopenia. Thrombocytopenia may develop or worsen during pregnancy. Women with type 2B VWD may present with thrombocytopenia during pregnancy [28,46–50]. In several cases, thrombocytopenia occurred only during pregnancy, with normal platelet counts documented after delivery [28,46–48,50]. The severity of thrombocytopenia varies, with nadir values occasionally as low as 10 000–20 000 mm^{-3} at term [20,46,47,49]. Thrombocytopenia may recur during subsequent pregnancies [28].

Thrombocytopenia during pregnancy reflects the increased production of variant VWF and resulting spontaneous platelet aggregation and turnover. Spontaneous platelet aggregation during pregnancy is inhibited by monoclonal antibodies directed against the platelet GPIb receptor and VWF, consistent with this mechanism [28,48]. The severity of thrombocytopenia reflects both the amount of variant VWF produced and the bone marrow's ability to increase platelet production. The concentration of variant VWF may be high enough to cause thrombocytopenia only during pregnancy, explaining the frequent normalization of platelet counts postpartum [28,49,50]. The extent to which thrombocytopenia contributes

to the bleeding risk is unknown but probably depends on the severity. The frequency of bleeding complications during pregnancy is also unknown because of the relative rarity of the disorder. There are multiple case reports of postpartum hemorrhage, usually, but not exclusively, in women who did not receive prophylactic therapy at delivery [14,22,28,47].

Women who present with thrombocytopenia during pregnancy may be misdiagnosed with idiopathic thrombocytopenic purpura, resulting in unnecessary and ineffective therapy [28,46,50]. Type 2B VWD should be included in the differential diagnosis of thrombocytopenia during pregnancy, especially in women with a personal or family history of abnormal bleeding (Table 2). FVIII, VWF antigen and activity levels may be normal during late pregnancy, with occasional values > 100% of normal [28,46]. However, the VWF activity level is often persistently low, and high-molecular-weight multimers are reduced or absent, even at term [20,28,48,50]. Increased platelet aggregation at low concentrations of ristocetin characteristic of type 2B disease was observed in the third trimester in the few case reports that included this testing during pregnancy [20,50]. DNA sequence analysis for the most common type 2B VWD mutations may confirm the diagnosis in uncertain cases. Spontaneous platelet aggregation (before the addition of platelet agonists) and clumping *in vitro* are also common during pregnancy. Automated machine platelet counts may underestimate the actual value in women with platelet clumping on a peripheral blood smear.

Neonatal complications

Infants with VWD are at risk from intracranial hemorrhage and from scalp hematomas during labor and vaginal delivery, especially with the use of invasive monitoring techniques, forceps or other instrumentation. Bleeding complications are only rarely reported, although most studies did not include information on neonatal outcome. In one series of 55 pregnancies there were no neonatal bleeding complications, even in the 11 cases that required invasive monitoring during labor [13]. Scalp hematomas, bleeding after intramuscular vitamin K injections, and umbilical bleeding are infrequent complications in affected infants [13,17]. There are several case reports of affected offspring of women with type 2B VWD with platelet counts of 10 000–20 000 mm^{-3} at birth without abnormal bleeding. One infant received a prophylactic VWF–FVIII concentrate and platelet transfusion shortly after birth [47,49]. Fetal bleeding complications during pregnancy are also rare. There is a single case report of a fetus with type 3 VWD in whom blood sampling by cordocentesis was complicated by feto–maternal hemorrhage, and fetal hypovolemia requiring an intracardiac blood transfusion [51]. In two other reports an intracranial hemorrhage and a subdural hematoma were discovered incidentally at 32 and 22 weeks, respectively, in two fetuses that were subsequently diagnosed with VWD [52,53].

Table 2 Type 2B von Willebrand disease during pregnancy

Laboratory findings	Range at term*
Thrombocytopenia	10 000–60 000 mm^{-3}
Bleeding time prolonged (or normal)	12–19 min
PFA – 100 closure time prolonged (or normal)	ND
FVIII activity (↑ or no change)	85–190%
VWF antigen (↑ or no change)	77–230%
VWF activity (no change or ↓ or ↑)	17–217%
Large multimers reduced or absent	–
Platelet aggregation at low concentrations of ristocetin	–
Spontaneous platelet aggregation†	–
Platelet clumping on peripheral blood smear	–
DNA sequence analysis of the A1 region of the VWF gene	–

↑ increased, ↓ decreased; PFA–100, platelet function analyzer; ND, not determined; VWF, von Willebrand factor; FVIII, factor VIII; *taken from references [14, 28, 46–50]; †before addition of platelet agonists.

Miscarriage

There is no evidence that VWD impairs fertility or increases the risk of miscarriage, even in women with severe type 3 disease [4,33,54]. The reported rates of spontaneous miscarriage in affected women (10–22%) [4,13,22], are similar to the estimated 10–20% incidence in the general population [55,56]. However prospective controlled comparative studies with age-matched normal women have not been performed. In a retrospective study, women with VWD who were interviewed by telephone reported a higher frequency of miscarriage (15%) than control women (9%), although the difference was of borderline significance ($P = 0.05$) [26]. Two other uncontrolled series reported similar overall spontaneous miscarriage rates of 21% and 22%, respectively [13,22]. In one study, all women with a history of miscarriage also had at least one successful pregnancy. Women with type 1 VWD had a higher miscarriage rate (32% of pregnancies) than those with type 2 and 3 disease (11% of pregnancies), suggesting that the bleeding disorder does not contribute to this adverse outcome [22]. Another large series of Iranian women with type 3 VWD found no evidence of an increased incidence of miscarriage, but did not provide specific data [33]. Although the use of FVIII concentrates to prevent early miscarriage has been anecdotally reported, there is no evidence that prophylactic therapy improves pregnancy outcome in women with prior fetal loss [21].

Genetic counseling and prenatal diagnosis

Genetic counseling about the risk of disease transmission and its variable expression should be provided for all women with VWD. This is particularly important for families with a child with type 3 VWD because each subsequent child has a 25% chance of inheriting a similar severe disorder. Since most patients with type 1 and 2 VWD have a mild or moderately severe bleeding disorder, prenatal diagnosis is usually consid-

ered only in pregnancies at risk for type 3 disease [57,58]. Prenatal diagnosis of VWD is performed by analysis of DNA extracted from fetal cells obtained by chorionic villus sampling at 10–12 weeks gestation or amniocentesis at 16–18 weeks gestation. In cases in which the causative mutation is unknown, analysis of restriction fragment length polymorphisms or variable number of tandem repeat sequences of the VWF gene are used to identify the mutant allele [57]. Although rarely performed, fetal blood samples obtained by cordocentesis at 18–20 weeks gestation can be used to measure VWF levels as well as for DNA analysis.

Treatment

Treatment options for VWD include DDAVP, VWF-containing blood products and other non-transfusional therapies such as anti-fibrinolytic agents and estrogens.

Desmospressin

Desmopressin (1-8-deamino-D-arginine vasopressin, DDAVP), a synthetic analog of vasopressin, increases plasma FVIII and VWF levels transiently in normal individuals and in patients with VWD. It is most effective in patients with type 1 disease, who have normal VWF available for release from storage sites. The efficacy and safety of DDAVP for prophylaxis or treatment of pregnancy-associated bleeding have not been systematically studied. Multiple anecdotal reports suggest that it is effective for prevention or control of bleeding at the time of abortion and delivery [14,16,19,23]. In one survey, 50% and 34% of hematologists reported using intravenous and intranasal DDAVP, respectively, for postpartum hemorrhage in women with type 1 VWD. Although there are no clinical trials confirming safety during pregnancy, only 31% of hematologists considered pregnancy a contraindication [59]. Concerns about the use of DDAVP antepartum are based on the potential risks of placental insufficiency (as a result of vasoconstriction), an oxytocic effect, and maternal and/or neonatal hyponatremia [60]. However, in contrast to naturally occurring vasopressin, DDAVP has minimal vasocontrictive and oxytocic effects, consistent with its predominant V_2 vasopressin receptor activity [61]. Intranasal DDAVP had no effect on uterine blood flow or vascular tone, as measured by Doppler ultrasound during treatment of women with intrauterine-device-associated menorrhagia [62]. A systematic review of DDAVP use during pregnancy for diabetes insipidus found no association with maternal hypertension, uterine hyperstimulation, prematurity, or neonatal low birth weight [63]. There are also no reports of hypertension or placental insufficiency with the higher doses used for bleeding disorders [17,23,64,65]. DDAVP had no effect on uterine contractions in five pregnant women who had continuous monitoring for 24 h after a 2-μg intravenous dose at term [66]. There are a few anecdotal reports of mildly increased uterine contractions after a higher dose (20 μg intravenous) in late pregnancy [67,68]. A woman with VWD developed preterm labor that was attributed to 'water retention' after a test dose in the third trimester [17]. However, DDAVP has been used in pregnant women with VWD and other bleeding disorders without premature labor or other complications [54,64,65]. There are no reports of an adverse drug interaction when DDAVP is given during or after an oxytocin infusion [63,64,69].

The risk of hyponatremia is the result of DDAVP's more potent and prolonged antidiuretic effect, compared to that of the natural hormone [61]. It is unknown whether pregnant women are more susceptible to DDAVP-induced hyponatremia as a result of altered osmoregulation and the decline in plasma sodium levels during normal pregnancy [16]. The combination of DDAVP and oral water loading acutely lowered sodium levels in pregnant sheep and pregnant women at term [66,70,71]. Two women with VWD developed clinically significant hyponatremia after receiving DDAVP in late pregnancy or postpartum, in one case complicated by a tonic/clonic seizure [17].

There are very few data on the potential fetal effects of DDAVP. DDAVP had no effect on fetal heart rate or outcome in five pregnant women who had continuous fetal monitoring after a 2-μg intravenous dose at term [66]. There were no neonatal complications attributed to the maternal use of DDAVP throughout pregnancy for diabetes insipidus [63], nor were there any complications reported in case reports of women with VWD or other bleeding disorders who received a dose during pregnancy [17,54,64,65,67,69]. Although the placental transport of DDAVP in pregnant women has not been studied, experimental and animal models suggest little or no transfer at the drug concentrations used in clinical practice. However, there is still a potential risk of fetal hyponatremia as a result of the maternal antidiuretic effect. DDAVP-induced hyponatremia in pregnant sheep produced a parallel decrease in fetal plasma sodium level, despite undetectable placental DDAVP transport [70,71]. The risk of fetal hyponatremia underscores the importance of avoiding excess water intake when DDAVP is used during pregnancy.

There are no studies confirming the safety of DDAVP during breastfeeding. A single case report found 'little change' in milk levels after a 10 μg intranasal dose, despite a 7-fold increase in maternal plasma levels [72]. The amount of DDAVP excreted into breast milk after the 10-fold to 30-fold higher doses used for VWD is unknown. However, the negligible oral absorption of DDAVP (0.16% of an oral dose) should result in minimal infant levels even at higher doses [73].

Transfusional therapy

Cryoprecipitate and VWF–FVIII concentrates have been used to prevent or control pregnancy-associated bleeding in women with VWD that is unresponsive to DDAVP [13,22,25,33]. Virally inactivated VWF–FVIII concentrates are the treatment of choice, because cryoprecipitate does not undergo virucidal treatment. Cryoprecipitate should not be used during pregnancy because of the small risk of transmission of viral or other blood-borne infections. It may be used in an emergency if

VWF–FVIII concentrates are not available. Immunopurified and recombinant FVIII products contain little or no VWF and are not an effective treatment for VWD.

Antifibrinolytic agents

Antifibrinolytic agents are usually avoided during pregnancy but have been used to control postpartum hemorrhage in women with VWD [13,21,22]. Although pregnant rodents and rabbits have received high doses without evidence of teratogenicity, the safety of these agents during pregnancy and lactation is not established. Women receiving tranexamic acid at delivery had umbilical cord levels approximately 70–80% of maternal levels, confirming human placental transport [74,75]. There are no studies of antifibrinolytic therapy during pregnancy in women with VWD. However, tranexamic acid has been used to control or prevent bleeding from placental abruption, Caesarean section, or other obstetric causes, without apparent maternal or fetal adverse effects [75–78]. Limited evidence suggests minimal excretion into breast milk, without adverse neonatal effects [79,80].

Conclusions

Women with VWD require monitoring during and after pregnancy. Although rare, antepartum hemorrhage may complicate spontaneous miscarriage or elective termination. Because of the rapid fall in FVIII and VWF levels after delivery, women with VWD are at substantial risk for postpartum hemorrhage. The risk is higher in those with type 2 and 3 disease and persists for several weeks after delivery. There is currently no consensus on the optimal management of women with VWD during pregnancy. Meticulous surgical hemostasis, effective uterine contraction and the avoidance of antiplatelet drugs will reduce the risk of postpartum hemorrhage. Women with type 3 VWD require VWF replacement at the time of delivery and postpartum. Most experts also recommend prophylaxis in those with persistently low FVIII and VWF levels ($< 50\%$) at term [3,32]. However, there are no data defining a threshold level of FVIII or VWF as a reliable predictor of bleeding. The limited evidence suggests that DDAVP use is relatively safe during pregnancy, although confirmatory studies are needed. Women who receive DDAVP should limit their fluid intake to reduce the risk of hyponatremia, especially after repeated doses. Women unresponsive to DDAVP or with other contraindications should receive a VWF–FVIII concentrate for prophylaxis or treatment of bleeding. Until more specific guidelines are defined by prospective trials, decisions about prophylaxis and epidural anesthesia require a careful risk–benefit assessment in each individual case. The optimal dose and duration of prophylactic therapy will depend on the type and severity of VWD, mode of delivery and clotting factor levels at term. The frequent observation that most postpartum hemorrhages occur after a reduction in dose or discontinuation of therapy underscores the importance of close monitoring for several weeks after delivery.

References

1 Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. *Blood* 1987; **69**: 454–9.
2 Werner EJ, Broxson EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. *J Pediatr* 1993; **123**: 893–8.
3 Sadler JE, Mannucci PM, Berntorp E, Bochkov N, Boulyjenkov V, Ginsburg D, Meyer D, Peake I, Rodeghiero F, Srivastava A. Impact, diagnosis and treatment of von Willebrand disease. *Thromb Haemost* 2000; **84**: 160–74.
4 Silwer J. von Willebrand's disease in Sweden. *Acta Paediatr Scand Suppl* 1973; **238**: 1–159.
5 Miller CH, Graham JB, Goldin LR, Elston RC. Genetics of classic von Willebrand's disease. I. Phenotypic variation within families. *Blood* 1979; **54**: 117–36.
6 Sie P, Caron C, Azam J, Goudemand J, Grandjean H, Boneu B, Foumie A. Reassessment of von Willebrand factor (VWF), VWF propeptide, factor VIII. C and plasminogen activator inhibitors 1 and 2 during normal pregnancy. *Br J Haematol* 2003; **121**: 897–903.
7 Clark P, Brennand J, Conkie JA, McCall F, Greer IA, Walker ID. Activated protein C sensitivity, protein C, protein S and coagulation in normal pregnancy. *Thromb Haemost* 1998; **79**: 1166–70.
8 Strauss HS, Diamond LK. Elevation of Factor Viii (antihemophilic factor) during pregnancy in normal persons and in a patient with von Willebrand's disease. *N Engl J Med* 1963; **269**: 1251–2.
9 Sanchez-Luceros A, Meschengieser SS, Marchese C, Votta R, Casais P, Woods AI, Nadal MV, Salviu MJ, Lazzari MA. Factor VIII and von Willebrand factor changes during normal pregnancy and puerperium. *Blood Coagul Fibrinolysis* 2003; **14**: 647–51.
10 Hanna W, McCarroll D, McDonald T, Painter P, Tuller J, Chen J, Lange R. Variant von Willebrand's disease and pregnancy. *Blood* 1981; **58**: 873–9.
11 Wickstrom K, Edelstam G, Lowbeer CH, Hansson LO, Siegbahn A. Reference intervals for plasma levels of fibronectin, von Willebrand factor, free protein S and antithrombin during third-trimester pregnancy. *Scand J Clin Lab Invest* 2004; **64**: 31–40.
12 Stirling Y, Woolf L, North WR, Seghatchian MJ, Meade TW. Haemostasis in normal pregnancy. *Thromb Haemost* 1984; **52**: 176–82.
13 Kadir RA, Lee CA, Sabin CA, Pollard D, Economides DL. Pregnancy in women with von Willebrand's disease or factor XI deficiency. *Br J Obstet Gynaecol* 1998; **105**: 314–21.
14 Ramsahoye BH, Davies SV, Dasani H, Rearson JF. Obstetric management in von Willebrand's disease: a report of 24 pregnancies and a review of the literature. *Haemophilia* 1995; **1**: 140–4.
15 Alperin JB. Estrogens and surgery in women with von Willebrand's disease. *Am J Med* 1982; **73**: 367–71.
16 Conti M, Mari D, Conti E, Muggiasca ML, Mannucci PM. Pregnancy in women with different types of von Willebrand disease. *Obstet Gynecol* 1986; **68**: 282–5.
17 Chediak JR, Alban GM, Maxey B. von Willebrand's disease and pregnancy: management during delivery and outcome of offspring. *Am J Obstet Gynecol* 1986; **155**: 618–24.
18 Greer IA, Lowe GD, Walker JJ, Forbes CD. Haemorrhagic problems in obstetrics and gynaecology in patients with congenital coagulopathies. *Br J Obstet Gynaecol* 1991; **98**: 909–18.
19 Castaman G, Eikenboom JC, Contri A, Rodeghiero F. Pregnancy in women with type 1 von Willebrand disease caused by heterozygosity for von Willebrand factor mutation C1130F. *Thromb Haemost* 2000; **84**: 351–2.
20 Casonato A, Sartori MT, Bertomoro A, Fede T, Vasoin F, Girolami A. Pregnancy-induced worsening of thrombocytopenia in a patient with type IIB von Willebrand's disease. *Blood Coagul Fibrinolysis* 1991; **2**: 33–40.
21 Caliezi C, Tsakiris DA, Behringer H, Kuhne T, Marbet GA. Two consecutive pregnancies and deliveries in a patient with von Willebrand's disease type 3. *Haemophilia* 1998; **4**: 845–9.

22 Foster PA. The reproductive health of women with von Willebrand disease unresponsive to DDAVP. results of an international survey. On behalf of the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the ISTH. *Thromb Haemost* 1995; **74**: 784–90.
23 Ito M, Yoshimura K, Toyoda N, Wada H. Pregnancy and delivery in patients with von Willebrand's disease. *J Obstet Gynaecol Res* 1997; **23**: 37–43.
24 Punnonen R, Nyman D, Gronroos M, Wallen O. Von Willebrand's disease and pregnancy. *Acta Obstet Gynecol Scand* 1981; **60**: 507–9.
25 Nitu-Whalley IC, Griffioen A, Harrington C, Lee CA. Retrospective review of the management of elective surgery with desmopressin and clotting factor concentrates in patients with von Willebrand disease. *Am J Hematol* 2001; **66**: 280–4.
26 Kirtava A, Drews C, Lally C, Dilley A, Evatt B. Medical, reproductive and psychosocial experiences of women diagnosed with von Willebrand's disease receiving care in haemophilia treatment centres: a case–control study. *Haemophilia* 2003; **9**: 292–7.
27 Ragni MV, Bontempo FA, Hassett AC. von Willebrand disease and bleeding in women. *Haemophilia* 1999; **5**: 313–17.
28 Rick ME, Williams SB, Sacher RA, McKeown LP. Thrombocytopenia associated with pregnancy in a patient with type IIB von Willebrand's disease. *Blood* 1987; **69**: 786–9.
29 Kouides PA, Phatak PD, Burkart P, Braggins C, Cox C, Bernstein Z, Belling L, Holmberg P, MacLaughlin W, Howard F. Gynaecological and obstetrical morbidity in women with type I von Willebrand disease: results of a patient survey. *Haemophilia* 2000; **6**: 643–8.
30 Kirtava A, Crudder S, Dilley A, Lally C, Evatt B. Trends in clinical management of women with von Willebrand disease: a survey of 75 women enrolled in haemophilia treatment centres in the United States. *Haemophilia* 2004; **10**: 158–61.
31 Federici AB. Mild forms of von Willebrand disease: diagnosis and management. *Curr Hematol Rep* 2003; **2**: 373–80.
32 Federici AB, Castaman G, Mannucci PM. Guidelines for the diagnosis and management of von Willebrand disease in Italy. *Haemophilia* 2002; **8**: 607–21.
33 Lak M, Peyvandi F, Mannucci PM. Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease. *Br J Haematol* 2000; **111**: 1236–9.
34 Hundegger R, Husslein P, Berghammer P, Egarter C, Kyrle A. Postpartum bleeding and von Willebrand's disease. *Arch Gynecol Obstet* 2002; **266**: 160–2.
35 Jones BP, Bell EA, Maroof M. Epidural labor analgesia in a parturient with von Willebrand's disease type IIA and severe preeclampsia. *Anesthesiology* 1999; **90**: 1219–20.
36 Milaskiewicz RM, Holdcroft A, Letsky E. Epidural anaesthesia and von Willebrand's disease. *Anaesthesia* 1990; **45**: 462–4.
37 Cohen S, Daitch JS, Amar D, Goldiner PL. Epidural analgesia for labor and delivery in a patient with von Willebrand's disease. *Reg Anesth* 1989; **14**: 95–7.
38 Lipton RA, Ayromlooi J, Coller BS. Severe von Willebrand's disease during labor and delivery. *JAMA* 1982; **248**: 1355–7.
39 Gu J, Jorieux S, Lavergne JM, Ruan C, Mazurier C, Meyer D. A patient with type 2N von Willebrand disease is heterozygous for a new mutation: Gly22Glu. Demonstration of a defective expression of the second allele by the use of monoclonal antibodies. *Blood* 1997; **89**: 3263–9.
40 Federici AB, Mazurier C, Berntorp E, Lee CA, Scharrer I, Goudemand J, Lethagen S, Nitu I, Ludwig G, Hilbert L, Mannucci PM. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. *Blood* 2004; **103**: 2032–8.
41 Dennis MW, Clough V, Toh CH. Unexpected presentation of type 2N von Willebrand disease in pregnancy. *Haemophilia* 2000; **6**: 696–7.
42 Nishino M, Nishino S, Sugimoto M, Shibata M, Tsuji S, Yoshioka A. Changes in factor VIII binding capacity of von Willebrand factor and factor VIII coagulant activity in two patients with type 2N von Willebrand disease after hemostatic treatment and during pregnancy. *Int J Hematol* 1996; **64**: 127–34.
43 Watanabe T, Minakami H, Sakata Y. Successful management of pregnancy in a patient with von Willebrand disease Normandy. *Obstet Gynecol* 1997; **89** (5 Part 2): 859.
44 Mazurier C, Dieval J, Jorieux S, Delobel J, Goudemand M. A new von Willebrand factor (vWF) defect in a patient with factor VIII (FVIII) deficiency but with normal levels and multimeric patterns of both plasma and platelet vWF. Characterization of abnormal vWF/FVIII interaction. *Blood* 1990; **75**: 20–6.
45 Mazurier C, Gaucher C, Jorieux S, Goudemand M. Biological effect of desmopressin in eight patients with type 2N ('Normandy') von Willebrand disease. *Collaborative Group Br J Haematol* 1994; **88**: 849–54.
46 Giles AR, Hoogendoorn H, Benford K. Type IIB von Willebrand's disease presenting as thrombocytopenia during pregnancy. *Br J Haematol* 1987; **67**: 349–53.
47 Mathew P, Greist A, Maahs JA, Lichtenberg EC, Shapiro AD. Type 2B vWD: the varied clinical manifestations in two kindreds. *Haemophilia* 2003; **9**: 137–44.
48 Pareti FI, Federici AB, Cattaneo M, Mannucci PM. Spontaneous platelet aggregation during pregnancy in a patient with von Willebrand disease type IIB can be blocked by monoclonal antibodies to both platelet glycoproteins Ib and IIb/IIIa. *Br J Haematol* 1990; **75**: 86–91.
49 Burlingame J, McGaraghan A, Kilpatrick S, Hambleton J, Main E, Laros RK. Maternal and fetal outcomes in pregnancies affected by von Willebrand disease type 2. *Am J Obstet Gynecol* 2001; **184**: 229–30.
50 Ieko M, Sakurama S, Sagawa A, Yoshikawa M, Satoh M, Yasukouchi T, Nakagawa S. Effect of a factor VIII concentrate on type IIB von Willebrand's disease-associated thrombocytopenia presenting during pregnancy in identical twin mothers. *Am J Hematol* 1990; **35**: 26–31.
51 Ash KM, Mibashan RS, Nicolaides KH. Diagnosis and treatment of feto-maternal hemorrhage in a fetus with homozygous von Willebrand's disease. *Fetal Ther* 1988; **3**: 189–91.
52 Mullaart RA, Van Dongen P, Gabreels FJ, van Oostrom C. Fetal periventricular hemorrhage in von Willebrand's disease: short review and first case presentation. *Am J Perinatol* 1991; **8**: 190–2.
53 Folkerth RD, McLaughlin ME, Levine D. Organizing posterior fossa hematomas simulating developmental cysts on prenatal imaging. report of 3 cases. *J Ultrasound Med* 2001; **20**: 1233–40.
54 Mannucci PM. How I treat patients with von Willebrand disease. *Blood* 2001; **97**: 1915–19.
55 Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC. Incidence of early loss of pregnancy. *N Engl J Med* 1988; **319**: 189–94.
56 Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril* 2003; **79**: 577–84.
57 Peake IR, Bowen D, Bignell P, Liddell MB, Sadler JE, Standen G, Bloom AL. Family studies and prenatal diagnosis in severe von Willebrand disease by polymerase chain reaction amplification of a variable number tandem repeat region of the von Willebrand factor gene. *Blood* 1990; **76**: 555–61.
58 Hoyer LW, Lindsten J, Blomback M, Hagenfeldt L, Cordesius E, Stromberg P, Gustavii B. Prenatal evaluation of fetus at risk for severe von Willebrand's disease. *Lancet* 1979; **2** (8135): 191–2.
59 Cohen AJ, Kessler CM, Ewenstein BM. Management of von Willebrand disease: a survey on current clinical practice from the haemophilia centres of North America. *Haemophilia* 2001; **7**: 235–41.
60 Kouides PA. Obstetric and gynaecological aspects of von Willebrand disease. *Best Pract Res Clin Haematol* 2001; **14**: 381–99.
61 Mannucci PM. Desmopressin: a nontransfusional form of treatment for congenital and acquired bleeding disorders. *Blood* 1988; **72**: 1449–55.

62 Mercorio F, De Simone R, Di Carlo C, Bifulco G, Tessitore G, Di Spiezio Sardo A, Nappi C. Effectiveness and mechanism of action of desmopressin in the treatment of copper intrauterine device-related menorrhagia: a pilot study. *Hum Reprod* 2003; **18**: 2319–22.
63 Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. *Obstet Gynecol Surv* 1998; **53**: 450–5.
64 Fragneto RY, Datta S. Epidural analgesia in a preeclamptic parturient after normalization of a prolonged bleeding time with DDAVP. *Reg Anesth* 1995; **20**: 448–51.
65 Weinbaum PJ, Cassidy SB, Campbell WA, Rickles FR, Vintzileos AM, Nochimson DJ, Tsipouras P. Pregnancy management and successful outcome of Ehlers–Danlos syndrome type IV. *Am J Perinatol* 1987; **4**: 134–7.
66 Ross MG, Cedars L, Nijland MJ, Ogundipe A. Treatment of oligohydramnios with maternal 1-deamino-[8-D-arginine] vasopressin-induced plasma hypoosmolality. *Am J Obstet Gynecol* 1996; **174**: 1608–13.
67 Rochelson B, Caruso R, Davenport D, Kaelber A. The use of prophylactic desmopressin (DDAVP) in labor to prevent hemorrhage in a patient with Ehlers–Danlos syndrome. *N Y State J Med* 1991; **91**: 268–9.
68 van der Wildt B, Drayer JI, Eskes TK. Diabetes insipidus in pregnancy as a first sign of a craniopharyngioma. *Eur J Obstet Gynecol Reprod Biol* 1980; **10**: 269–74.
69 Zatik J, Poka R, Borsos A, Pfliegler G. Variable response of Hermansky–Pudlak syndrome to prophylactic administration of 1-desamino 8D-arginine in subsequent pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2002; **104**: 165–6.
70 Roberts TJ, Nijland MJ, Curran M, Ross MG. Maternal 1-deamino-8-D-arginine-vasopressin-induced sequential decreases in plasma sodium concentration: ovine fetal renal responses. *Am J Obstet Gynecol* 1999; **180** (1 Part 1): 82–90.
71 Ross MG, Nijland MJ, Kullama LK. 1-Deamino-[8-D-arginine] vasopressin-induced maternal plasma hypoosmolality increases ovine amniotic fluid volume. *Am J Obstet Gynecol* 1996; **174**: 1118–25; discussion 1125–7.
72 Burrow GN, Wassenaar W, Robertson GL, Sehl H. DDAVP treatment of diabetes insipidus during pregnancy and the post-partum period. *Acta Endocrinol (Copenh)* 1981; **97**: 23–5.
73 Hale TW. *Medications and Mother's Milk*. Pharmasoft Publishing: Amarillo, TX, USA, 2002: 201–2.
74 Kullander S, Nilsson IM. Human placental transfer of an antifibrinolytic agent (AMCA). *Acta Obstet Gynecol Scand* 1970; **49**: 241–2.
75 Walzman M, Bonnar J. Effects of tranexamic acid on the coagulation and fibrinolytic systems in pregnancy complicated by placental bleeding. *Arch Toxicol Suppl* 1982; **5**: 214–20.
76 Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of thrombo-embolic complications. *Thromb Haemost* 1993; **70**: 238–40.
77 Svanberg L, Astedt B, Nilsson IM. Abruptio placentae – treatment with the fibrinolytic inhibitor tranexamic acid. *Acta Obstet Gynecol Scand* 1980; **59**: 127–30.
78 Gai MY, Wu LF, Su QF, Tatsumoto K. Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial. *Eur J Obstet Gynecol Reprod Biol* 2004; **112**: 154–7.
79 Verstraete M. Clinical application of inhibitors of fibrinolysis. *Drugs* 1985; **29**: 236–61.
80 DRUGDEX Editorial Staff. Desmopressin (Drug Monograph). In: *MICROMEDIX*. Greenwood Village, CO, Thomson, 2004.