Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum

Panagiotis Peitsidis† & Rezan A Kadir
The Royal Free Hospital, Haemophilia Centre & Thrombosis Unit, Department of Obstetrics and Gynaecology, London, UK

Objective: The aim of this study is critically to review the available evidence regarding the use, efficacy and safety of tranexamic acid in the management of hemorrhage during pregnancy and for prevention and treatment of postpartum hemorrhage.

Research design and methods: We performed a systematic search of electronic literature (PubMed, Embase, CINAHL, Scopus, Cochrane, DARE) to review all studies looking at the use of tranexamic acid during pregnancy and puerperium. We did a meta-analysis on three randomized controlled trials that evaluated reduction in blood loss in women undergoing cesarean sections with the use of tranexamic acid.

Results: An electronic search yielded 34 articles, the studies dating from 1976 to 2010, five randomized controlled trials, seven observational studies, and twenty-two case reports. Meta-analysis showed that the estimate of the combined effect of tranexamic acid compared with placebo was a difference of 32.5 ml reduction in blood loss (95% CI -4.1 - 69.13; p = 0.08). Tranexamic acid was also used successfully to prevent and treat bleeding in observation studies and case reports. Pulmonary embolism was reported in two cases; however, the possible involvement of tranexamic acid in these thrombotic episodes could neither be confirmed nor excluded.

Conclusions: The clinical studies suggest that tranexamic acid reduces the amount of blood loss after delivery during cesarean sections and vaginal deliveries, and reduces the requirement for blood transfusion. Tranexamic acid seems to be safe and effective in the prevention and management of bleeding during pregnancy. Further investigation and larger clinical trials with better design and methodological quality are required to confirm these findings.

Keywords: hemorrhage, postpartum, pregnancy, tranexamic acid
be formed under these circumstances, it is unable to bind to and degrade fibrin [3]. Tranexamic acid is 6 – 10 times more potent in vitro in terms of binding to plasminogen/plasmin than the other synthetic antifibrinolytic agent e-aminocaproic acid (EACA) [3]. Owing to its antifibrinolytic effect, clinicians are reluctant to use tranexamic acid during pregnancy because of potential risk of thromboembolism in the mother and the fetus/newborn. The FDA’s pregnancy category for tranexamic acid is Category B, as animal reproduction studies have not demonstrated a fetal risk, but no studies in pregnant women are available. Tranexamic acid crosses the placenta. However, its lack of effect on plasminogen activator activity in the vascular cell wall protects the fetus and newborn from potential thromboembolic complications [4]. Postpartum hemorrhage (PPH) remains a significant contributor to maternal morbidity and mortality throughout the world. Similarly, bleeding during pregnancy is associated with adverse maternal and perinatal outcome. Tranexamic acid has been proposed and used for prevention and management of antepartum and postpartum hemorrhage. The aim of this study is to critically review the available evidence regarding the use, efficacy and safety of tranexamic acid in the management of hemorrhage during pregnancy and for prevention and treatment of PPH.

2. Materials and methods

2.1 Identification of literature

We searched the following computerized databases to identify the clinical reports related to the use of tranexamic acid during pregnancy and postpartum in the management of hemorrhagic conditions: MEDLINE (1966 to May 2010), EMBASE (1980 to May 2010), CINAHL (1981 to May 2010), SCOPUS (1966 to May 2010), Cochrane Library (2007 – 2010) and DARE (Database of Abstracts of Reviews of Effects; 1994 to May 2010). No language and time restrictions were imposed. The combination of terms as Medical Subject Headings (MeSH) for the database search was: (Tranexamic acid OR AMCA OR Cyclokapron) AND (pregnancy OR gestation). The last search was updated in June 2010, and all bibliographies of identified articles were examined for any unidentified articles from the electronic search. Abstracts from relevant conferences or scientific meetings were hand-searched for unpublished studies. The quality or characteristics of the included studies did not influence their eligibility for inclusion in the systematic review.

2.2 Study selection

Randomized clinical trials, nonrandomized observational studies, case series and case reports reporting the administration of tranexamic acid for the management of obstetric hemorrhage during pregnancy and post-partum up to 6 months were identified. Studies were considered eligible only if they reported the use of tranexamic acid during pregnancy and post-partum. Articles dealing with the use of tranexamic acid in nonpregnant women for the treatment of gynecological hemorrhage and studies reporting administration of tranexamic acid before pregnancy were excluded. Studies were selected in a two-stage process. First, two reviewers (PP and RAK) independently scrutinized the titles and the abstracts of the potentially relevant articles, and the citations of the manuscripts that were likely to be eligible were examined. Second, the manuscripts were examined in full text for inclusion or exclusion according to the aforementioned criteria. Two reviewers (PP and RAK) examined independently the English-language manuscripts; non-English manuscripts were examined by people that had command of the relevant language. Any disagreements were discussed and resolved by consensus of the participating authors or by arbitration of a third independent reviewer.

2.3 Data extraction

From each eligible randomized trial, we extracted data on the following items: country of the study, study design, number of patients allocated to groups, type of intervention, the age of participants, the dosage and route of administration and outcome measures – blood loss (mean and standard deviation in milliliters) in the randomized groups, p value and the presence of adverse effects. For blood loss volume, the difference in means (expressed in milliliters) was calculated with 95% confidence interval).

We assessed the methodological quality of the randomized trials by using the data about allocation concealment; the studies were evaluated according to the scale assigned by Schulz [5].

- A: Trials that have taken measures that ensure allocation concealment (central randomization; serially numbered, opaque, sealed envelopes; or other description with convincing elements of concealment)
- B: Trials in which allocation concealment is not reported at all or the authors report an approach that does not fall into one of the other categories
- C: Trials in which concealment is inadequate (such as alternation or reference to case record numbers or dates of birth)

In addition we collected information on the adequacy of randomization, blinding, the existence of placebo groups and intention-to-treat analysis, if applied.

From each eligible prospective study and case report, we recorded and tabulated the following items: authors’ names, country of study, design of the study, number of patients enrolled, age of patients, indication for administration of tranexamic acid, (antepartum, postpartum hemorrhage, placental abruption, coagulopathy), week of administration, concomitant diseases, dosage-route and duration of administration, platelet count if available, the quantity of blood loss if provided, adverse effects, the response-outcome measures to the hemostatic treatment and the use of any additional treatment. The response-outcome measure to treatment was...
evaluated according to the authors’ report; the overall response to tranexamic-acid treatment was subjectively defined by the authors as ‘Stopped’ when hemorrhage was controlled immediately after the initial administration of tranexamic acid, as ‘Gradually stopped’, if it was necessary to provide longer treatment and higher doses of tranexamic acid and as ‘Not stopped’ when it was necessary to offer aggressive surgical or invasive management in cases when hemorrhage could not be managed satisfactorily with tranexamic acid. Pregnancy outcome was defined as ‘Good’ with uneventful maternal and neonatal outcomes and as ‘Complicated’ if neonatal or maternal mortality were reported or the patient was subjected to hysterectomy or other surgical management.

We assessed the quality of the observational studies, case series and case reports via the Scottish Intercollegiate Guidelines Network (SIGN) [6].

- 2++ High-quality systematic reviews of case-control or cohort studies high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
- 2 + Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
- 2 - Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
- 3 Nonanalytic studies, e.g., case reports, case series

The highest level of evidence was provided by the randomized trials and the lowest quality of evidence was provided by the observational studies, case series and case reports.

3. Statistical analysis

The results from the randomized trials found were combined using a forest plot. Using the means, the standard deviations and the number in each group extracted from the appropriate studies, the overall mean difference between the groups and its standard error was calculated. A test for heterogeneity was performed, and depending on the results, a random effect was used to calculate a summary estimate of the difference between groups using the DerSimonian and Laird method or a fixed effect model was used, using the Mantal Haenszel method. Statistical analysis was performed using the statistical software Stata v10.1 (StataCorp, Stata Statistical Software, College Station, Texas, USA).

4. Results

The flowchart diagram of the study selection is outlined in Figure 1. Initially, the electronic web searches yielded 420 items: 74 from PubMed, 18 from Embase, 81 from CINAHL, 231 from Scopus 14 from Cochrane Library 2 and from DARE. Of those, 24 studies were excluded on basis of duplication, and 354 studies were not eligible and excluded on the basis of irrelevance. A total of 42 studies were retrieved and scrutinized in full text, of which seven were excluded because of the use of tranexamic acid before pregnancy, and use in nonhemorrhagic conditions. Finally, 35 articles were included in the review: studies dated from 1976 to November 2010. In more detail, six articles were randomized control trials, seven were observational non-randomised studies, and 22 were case reports. The articles originated mainly from Europe (n = 26) and from Asia (n = 8), with one article from Oceania. We assessed articles written in English, Chinese, Russian, Danish and Polish. In total, 3235 patients were enrolled in the various studies, of which 912 actually received tranexamic acid and formed the clinically evaluable population.

5. Design and quality of the randomized control trials

The main characteristics and the quality of the controlled trials enrolled in the review are summarized in Table 1. Three randomized trials were multicenter [7-9] and three trials [10-12] were done in single institution centers. A total of 959 women were enrolled in the six trials [7,8,10-13].

One trial had a four-arm design [7] and five had a two-arm design [8,10-13]. In three studies the allocation concealment was not reported [7,8,10,11] and in three studies [10,12,13] it was inadequate. The methodology of randomization was defined in all the studies. In two studies, sequence was computer generated [7,12], in three studies [10,11,13] the sequence was defined by the rule of even and odds, and in the study by Gai et al. [8] the authors used consecutive number charts. No blinding and no intention-to-treat analysis (ITT) were reported in all of the randomized studies.

In two trials [8,11], tranexamic acid was administered intravenously 10 min before cesarean section, while in another trial [10], tranexamic acid was given intravenously 20 min before cesarean section. Dosage of administration was 1 g in all cases, and all patients were primigravidas. Cardinal vital signs – blood pressure, heart rate and respiratory rate – were not affected by tranexamic acid administration in study groups in all three studies [8,10,11]. Calculation of the quantity of blood loss in these three studies was performed after placental delivery and 2 h postpartum; this methodology does not take into account amniotic fluid quantity and blood loss before placental delivery. The formula for calculation of the blood loss was the following: (weight of used materials + unused materials - weight of all materials prior to surgery)/1.05, added to the blood volume in the suction container after placental delivery [8,10]. The cardinal finding of these trials was that post-operative blood loss was significantly reduced in the study group (p = 0.001) [8,10]. Gai et al. [8] reported that transient mild adverse effects were observed. However, the type of adverse effects and the number of participants affected were
not provided; in the remaining trials no adverse effects were noted; and the neonatal and maternal outcome in all three studies was uneventful.

Another article provided data about the use of tranexamic acid in reducing postpartum blood loss after normal vaginal delivery in primigravid mothers [7]. The study population was randomized to four groups: group I received 1 g tranexamic acid, group II received 0.5 g tranexamic acid, group III received AMBA (aminomethylbenzoic acid), and group IV was the placebo group. A single intravenous dose of study medication was given before shoulder delivery. Postpartum blood loss was reduced in groups I and II (p < 0.001) [7]. Maternal and neonatal outcome was uneventful only two patients developed nausea (Table 1).

Ducloy-Bouthors et al. [13] used tranexamic acid for early management of postpartum hemorrhage (blood loss > 800 ml) after vaginal delivery in a randomized controlled trial in 144 women. Blood loss was measured at four time points: inclusion (T1), T1 + 30 min (T2), T1 + 2 h (T3), and T1 + 6 h (T4). The study reported that blood loss was
Table 1. Characteristics of the randomized trials.

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Study groups</th>
<th>Age (years)</th>
<th>Interventions</th>
<th>Dosage/route/ duration</th>
<th>Outcome measures</th>
<th>P value</th>
<th>Adverse effects</th>
<th>Schulz score</th>
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<tr>
<td>Vaginal delivery</td>
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<tr>
<td>Yang et al. (2001) [7]</td>
<td>China</td>
<td>Multicenter, comparative, randomized</td>
<td>n = 400 primiparas</td>
<td>n = 94 (study) n = 92 (study) n = 87 (placebo)</td>
<td>27.6 ± 2.9 27 ± 2.6 28 ± 2.6</td>
<td>Infusion of TA after delivery of fetal shoulders in the first 2 groups and infusion of AMBA in the 3rd group. Measurement of PP blood loss in ml Infusion of TA in women PP</td>
<td>1 g i.v. 0.5 g i.v. 0.5 gr i.v.</td>
<td>2 h &gt; PP/243.3 ml vs &lt; 0.01</td>
<td>Nausea</td>
<td>n = 2</td>
<td>B</td>
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<tr>
<td></td>
<td>Bouthors et al., 2010 [13]</td>
<td>France</td>
<td>Prospective, randomized, case controlled</td>
<td>n = 144</td>
<td>n = 72 (study) n = 72 (placebo)</td>
<td>NS</td>
<td></td>
<td>1 g in 1 h i.v. 1 gr/h over 6 h i.v.</td>
<td>2 h PP/46% reduction of blood loss and bleeding time 31 vs 65 min</td>
<td>0.0026</td>
<td>Transient</td>
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<td>Cesarean section</td>
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<tr>
<td>Gai et al. (2004) [8]</td>
<td>China</td>
<td>Multicenter, prospective, randomized, case controlled</td>
<td>n = 180 primiparas</td>
<td>n = 91 (study) n = 89 (placebo)</td>
<td>29.71 ± 4.18 29.75 ± 4.01</td>
<td>Infusion of TA 10 min before CS and measurement of PP blood loss in ml Infusion of TA in women PP</td>
<td>1 g i.v. &gt; 5 min</td>
<td>2 h &gt; CS/42.75 ± 40.45 ml vs 73.98 ± 77.09 ml</td>
<td>0.001</td>
<td>Transient</td>
<td>B</td>
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<tr>
<td></td>
<td>Gohel et al. (2007) [10]</td>
<td>India</td>
<td>Prospective, randomized, case controlled</td>
<td>n = 100 primiparas/ multiparas</td>
<td>n = 50 (study) n = 50 (placebo)</td>
<td>24.30 ± 3.65 24.89 ± 3.99</td>
<td>Infusion of TA 20 min before CS and measurement of PP blood loss in ml</td>
<td>1 g i.v. &gt; 5 min</td>
<td>2 h &gt; CS/75.71 ± 20.02 ml vs 133.03 ± 14.68 ml</td>
<td>0.001</td>
<td>NS</td>
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<td></td>
<td>Sekhavat et al. (2009) [11]</td>
<td>Iran</td>
<td>Prospective, randomized, case controlled</td>
<td>n = 90 primiparas</td>
<td>n = 45 (study) n = 45 (placebo)</td>
<td>26.2 ± 4.7 27.1 ± 4.1</td>
<td>Infusion of TA 10 min before CS and measurement of PP blood loss in ml</td>
<td>1 gr i.v. &gt; 5 min</td>
<td>2 h &gt; CS/28.0 ± 5.5 ml vs 37.1 ± 19.0 ml</td>
<td>0.000</td>
<td>NS</td>
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<td>Recurrent miscarriages</td>
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<tr>
<td>Tetruashvili et al. (2007) [12]</td>
<td>Russia</td>
<td>Prospective, randomized, case controlled</td>
<td>n = 80</td>
<td>n = 40 (study) n = 40 (placebo)</td>
<td>32.1 ± 2.6 31.2 ± 2.5</td>
<td>Administration of TA in women with history of miscarriages and calculation of frequency of bleeding by days</td>
<td></td>
<td>750 mg p.o. 7 days 2.1 ± 0.2 vs 5.6 ± 0.3 days</td>
<td>&lt; 0.01</td>
<td>NS</td>
<td>C</td>
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</table>

CS: Cesarean section; AMBA: Aminobenzoic acid; PP: Post-partum; NS: Not stated; TA: Tranexamic acid; i.v.: Intravenous; p.o.: per os.
Tranexamic acid in pregnancy and postpartum

46% lower between T2 and T3 (p = 0.026), and 49% lower between T2 and T4 (p = 0.0012); bleeding duration was shorter 31 ± 28 vs 65 ± 95 min (p = 0.004). Transient visual and digestive side effects were observed more frequently in the tranexamic acid group (17 vs 4, p = 0.028) [13].

The last randomized trial by Tetruashvili [12] used tranexamic acid to arrest bleeding in women with recurrent miscarriages and threatened miscarriages. Administration dosage ranged from 750 to 1500 mg, and duration of treatment ranged for 5 – 7 days from 5 to 22 weeks of pregnancy. No maternal and neonatal adverse effects were observed, and a significant reduction of duration of bleeding episodes was noted in the study group (p < 0.001). The clinical characteristics are summarized in Table 1.

We did a meta-analysis of three studies that reported the administration of tranexamic acid before cesarean sections to reduce postpartum bleeding. The estimate of the combined effect of tranexamic acid compared with placebo in the randomized, controlled trial (RCT) was a difference of 32.5 ml reduction of blood loss (95% CI -4.1 to 69.13; p = 0.08).

As there was evidence of significant heterogeneity between the three RCTs (p < 0.0001), a random effects model was used. The forest plot is shown in Figure 2.

6. Observational studies

Six observational nonrandomized studies [14-19] and one case series [20] were considered for inclusion in this review. Only one study was multicenter [17] and the remaining six were done in single institutions. The data regarding the characteristics and the outcome of the studies are outlined in Table 2.

In three studies, tranexamic acid was used to prevent bleeding: in one study after laser cervical conisation during pregnancy [16] and in two studies to prevent PPH in women with Factor XI (FXI) deficiency [21,22]. Four studies used tranexamic acid for antepartum bleeding [14,15,17,20]. In the study by Singh et al. [20] tranexamic acid was also used to control postpartum bleeding in one patient. Antepartum bleeding occurred after > 24 weeks of pregnancy (range 24 – 40 weeks), causes of bleeding were placental abruption [14,17] and placenta previa [15,17,20]. Walzman et al. [15] reported placenta previa as cardinal cause of bleeding in 3 cases out of 12; in the remaining nine cases the etiology of bleeding was not reported or identified. The fifth study by Békassy et al. [16] reported the administration of tranexamic acid as prophylaxis for bleeding in pregnant women undergoing cervical conisation. Two studies [22,18] used tranexamic acid prophylactically in pregnant patients with FXI deficiency. Dosage and duration of administration of tranexamic acid ranged from 1 to 4 g and duration of treatment from 1 day to 12 weeks.

In the study by Walzman et al. [15], the authors examined several coagulation parameters (plasminogen, antiplasmin, antithrombin III and factor VIII) in the maternal blood, 3 – 4 h after ingestion of tranexamic acid tablets. They showed a decrease in the fibrinolytic activity associated with a reduction of plasminogen and antiplasmin, while antithrombin III and Factor VIII were increased in the serum. In the study by Svanberg et al. [14] a reduction of plasminogen was also demonstrated.

Among the observational studies, tranexamic acid was used in 388 women during pregnancy. The indication was prophylaxis as a hemostatic agent to prevent bleeding during cervical conisation in 45 women [16]. In the remaining 343 women [14,15,17,20], tranexamic acid was used for management of antepartum hemorrhage (placental abruption, placenta previa and bleeding of unknown cause in 259, 71 and 13 women, respectively). Adverse effects were reported in the study by Lindoff et al. [17]. Two patients in the study group were diagnosed with pulmonary embolism. The first patient received tranexamic acid 3 g for 61 days before 35 gestational weeks for placenta previa, and the second patient received tranexamic acid 4 g for 15 days before 26 gestational weeks for placental abruption. Similarly, in the control group (not receiving tranexamic acid), one patient developed pulmonary embolism and three patients had deep vein thrombosis. With regard to the neonatal outcome, two neonates expired. The neonatal deaths were thought to be related to the acute hemorrhagic complications of placental abruption and not considered as an adverse effect of tranexamic acid.

In the rest of the studies no neonatal complications occurred.

The level of evidence provided were graded 2 + for four studies [14,15,17,23], 2- for two studies [16,24], and three for one study [20].

7. Case reports

The data regarding the characteristics and outcome of the case reports are presented in Table 3. The reports dated from 1976 [25] to 2010 [26], and the age of patients ranged from 16 to 39 years [27,28]. The majority of the cases reported management of postpartum hemorrhage with tranexamic acid [29,30,27,31-37,26]. Seven studies reported antepartum hemorrhage [25,38-43]. Hemorrhage associated with hematological disorders was reported in nine cases [44-29,30,31,28,35-37]. The most common hematological disorder mentioned was Bernard Soulier syndrome [29,34-36], followed by hemophilia [30,33], leukemia [28], other platelet disorders such as Glanzmann’s thrombasthenia [44], Evan’s syndrome [31], and platelet storage pool disease [37]. Tranexamic acid was given as treatment of induced coagulopathy amphetamine intoxication [45], postpartum hemorrhage [32], and amniotic fluid embolism [42,26].

Dosage of tranexamic acid ranged from 500 mg [35] to 6 g i.v. [38]. Duration of treatment ranged from 1 day to 64 days [25]. Treatment was provided from 21 weeks to 36 weeks of gestation [25,41]. Nine studies provided information about the amount of blood loss (range 1000 – 19 000 ml) [27,46,41,42,33,35-37,43]. However, information about how blood loss was estimated was unclear in all the reported studies. In 13 women (56.5% of all
case reports), the authors reported that hemorrhage ‘gradually stopped’ with additional management or prolonged treatment [25,38,44,29,39,27,28,40-42,36,26]. In five women (21.7%) the hemorrhage ‘stopped’ [30,45,34,35,37] and in five women the hemorrhage was defined as ‘not stopped’ (21.7%) [46,32,33,37,43]. In total, from all 22 case reports one adverse effect, pulmonary embolism, was reported; the patient received tranexamic acid 4 g for 10 days before 28 gestational weeks as treatment of placental abruption; pulmonary embolism was managed with streptokinase infusion and pregnancy was uneventful [39]. One patient expired because of extensive bleeding caused by amniotic fluid embolism [26]. No evidence about teratogenesis or adverse effects in fetuses and neonates was reported. All studies were graded 3 according to (SIGN).

8. Discussion

Tranexamic acid has been safely used for various clinical situations with beneficial effects. Tranexamic acid has been shown to reduce the perioperative blood loss and transfusion requirements in patients undergoing cardiac surgery with cardiopulmonary bypass, liver transplantation and transurethral prostatic surgery [3]. Tranexamic acid has also been applied in orthopedics for reduction of blood loss in corrective spinal surgery and knee prostatic surgical interventions [47,48]. Non-surgical uses of tranexamic acid include management of bleeding associated with leukemia, ocular bleeding, recurrent hemoptysis, hereditary angioneurotic angio-edema [49,50,47]. For women, tranexamic acid has been used successfully to reduce blood loss and blood transfusion requirements in management of several clinical conditions in gynecology including menorrhagia, interventional surgical procedures such as cervical conisation, and myomectomy [51-54,23,24,55,56]. The present systematic review suggests that tranexamic acid can reduce blood loss in several hemorrhagic conditions during pregnancy, and reduce postpartum bleeding.

Postpartum hemorrhage (PPH) has been defined as blood loss in excess of 500 ml after a vaginal birth, and more than 1000 ml after a cesarean delivery [57,58]. Primary PPH is defined as bleeding from the genital tract of 500 ml or more in the first 24 h after the delivery of the newborn, and secondary PPH occurring after 24 h of delivery, but before 6 weeks [57,58]. The incidence of PPH varies greatly depending on the criteria that are used to define it; typical estimates been have reported as ~ 4 – 6% [57,59,60]. In a systematic review [60] including 224 datasets from different regions around the world, an overall prevalence of PPH (defined as blood loss in excess of 500 ml) was reported to be 6.09% (95% CI 6.06 – 6.11). However, when the blood loss was measured objectively, the rate was 10.6%. PPH is considered the leading cause of pregnancy-related deaths worldwide, with an estimated 140 000 women dying annually from this complication, equating to one every 4 min. In addition, PPH is associated with a significant maternal morbidity including anemia and risks of blood transfusions. Ferrer et al. [21] did a meta-analysis on the use of tranexamic acid for reduction of postpartum blood loss. The authors assessed three studies; one with vaginal delivery [7] and two with cesarean section [8,10]. Combining the results of the three trials, the use of tranexamic acid significantly reduced mean blood loss by

<table>
<thead>
<tr>
<th>Study</th>
<th>Gohel (7) 2004</th>
<th>Gohel (8) 2007</th>
<th>Sekhavat (9) 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>91</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>89</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Weight</td>
<td>31.23 (13.19, 49.27)</td>
<td>57.32 (50.44, 64.20)</td>
<td>9.10 (6.03, 12.17)</td>
</tr>
</tbody>
</table>

Overall (I-squared = 98.7%, p = 0.000)

![Figure 2. Meta-analysis of randomized controlled trials of tranexamic acid versus placebo during cesarean section for reduction of postpartum blood loss.](image-url)
Table 2. Characteristics of the observational studies and case series of pregnant women treated with tranexamic acid during pregnancy and postpartum.

<table>
<thead>
<tr>
<th>Study [ref.]</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size</th>
<th>Mean age</th>
<th>Indications for treatment with TA</th>
<th>Weeks</th>
<th>Dosage/route</th>
<th>Duration of treatment</th>
<th>Response</th>
<th>Adverse effects, level of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svanberg et al. (1980) [14]</td>
<td>Sweden</td>
<td>Prospective, nonrandomized</td>
<td>73 women</td>
<td>NS</td>
<td>Antepartum hemorrhage (placental abruption)</td>
<td>26 – 40</td>
<td>1 g i.v. in all patients at 'acute phase' of the hemorrhage. 6 patients received 4 g p.o. for 1 – 12 wks until delivery</td>
<td>1 - 12 wks</td>
<td>No patient had bleeding diathesis</td>
<td>No, 2+</td>
</tr>
<tr>
<td>Walzman et al. (1982) [15]</td>
<td>Ireland</td>
<td>Prospective, nonrandomized</td>
<td>12 women</td>
<td>NS</td>
<td>Antepartum hemorrhage</td>
<td>24 – 36</td>
<td>3 g p.o.</td>
<td>7 days</td>
<td>No patient had bleeding diathesis</td>
<td>No, 2+</td>
</tr>
<tr>
<td>Bekassy et al. (1990) [16]</td>
<td>Sweden</td>
<td>Prospective, nonrandomized</td>
<td>45 women</td>
<td>NS</td>
<td>Hemostasis after laser cervical conisation</td>
<td>NS</td>
<td>1 g i.v. before surgery + 1 g in surgery + 1 g after surgery</td>
<td>14 days</td>
<td>No patient had bleeding diathesis</td>
<td>No, 2-</td>
</tr>
<tr>
<td>Lindoff et al. (1993) [17]</td>
<td>Sweden</td>
<td>Prospective, nonrandomized</td>
<td>256 women</td>
<td>NS</td>
<td>Antepartum hemorrhage, 186 for placental abruption, 68 for placenta previa</td>
<td>NS</td>
<td>3 g daily</td>
<td>152 women &gt; 3 days, 104 women &gt; 7 days</td>
<td>No patient had bleeding diathesis</td>
<td>2 patients developed pulmonary embolism after 61 days and 15 days of treatment respectively 4 patients developed embolism in the control group (no TA) OR = 3.6, 95% CL, p &gt; 0.16 (not significant statistically)</td>
</tr>
<tr>
<td>Singh et al. (2003) [20]</td>
<td>UK</td>
<td>Case series</td>
<td>3 women</td>
<td>1st 25</td>
<td>Primary PPH</td>
<td>Postpartum 30</td>
<td>1 g i.v.</td>
<td>1 day</td>
<td>Stopped</td>
<td>No, 3</td>
</tr>
<tr>
<td>Chi et al. (2009) [18]</td>
<td>UK</td>
<td>Prospective, nonrandomized</td>
<td>8 women</td>
<td>2nd 28</td>
<td>Antepartum hemorrhage</td>
<td>During labor 30</td>
<td>3 g i.v. daily</td>
<td>3 – 5 days</td>
<td>NS</td>
<td>No, 2+</td>
</tr>
<tr>
<td>Chi et al. (2009) [19]</td>
<td>UK</td>
<td>Prospective, nonrandomized</td>
<td>12 women</td>
<td>3rd 30</td>
<td>Antepartum hemorrhage</td>
<td>Antepartum 34</td>
<td>NS</td>
<td>NS $</td>
<td>NS</td>
<td>No, 2-</td>
</tr>
</tbody>
</table>

PPH and 2 secondary (late) PPH occurred despite prophylaxis.

*Scottish Intercollegiate Guidelines Network (SIGN).

In 11 of these the mother had a positive bleeding history, and in one case tranexamic acid was given in view of a cesarean delivery. However, 1 primary (early).

CL: Confidence level; i.v.: Intravenous; NS: Not stated; OR: Odds ratio; p.o.: per os; PPH: Postpartum hemorrhage; TA: Tranexamic acid.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Age (years)</th>
<th>Indication (symptomatology)</th>
<th>Concomitant disease</th>
<th>PLT count</th>
<th>Blood loss (ml)</th>
<th>Weeks (period)</th>
<th>Dosage of TA</th>
<th>Duration</th>
<th>Additional treatment</th>
<th>Adverse effects</th>
<th>Response</th>
<th>Pregnancy outcome, level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storm et al. (1976) [25]</td>
<td>Denmark</td>
<td>NS</td>
<td>Vaginal bleeding</td>
<td>No</td>
<td>NS</td>
<td>NS</td>
<td>21</td>
<td>4 g p.o.</td>
<td>64 days</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Good, 3</td>
</tr>
<tr>
<td>Astedt et al. (1978) [38]</td>
<td>Sweden</td>
<td>NS</td>
<td>Placental abruption</td>
<td>No</td>
<td>Normal</td>
<td>NS</td>
<td>26</td>
<td>6 g i.v. + 4 g p.o.</td>
<td>3 days</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Good, 3</td>
</tr>
<tr>
<td>Sundqvist et al. (1981) [44]</td>
<td>Sweden</td>
<td>35</td>
<td>Coagulopathy</td>
<td>Glanzmann's thrombasthenia</td>
<td>110 × 10^9 L</td>
<td>NS</td>
<td>35</td>
<td>1 day</td>
<td>PLT + uterotonics</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Good, 3</td>
</tr>
<tr>
<td>Heslop et al. (1986) [29]</td>
<td>Sweden</td>
<td>26</td>
<td>Secondary PPH</td>
<td>Bernard Soulier's</td>
<td>57 × 10^9 L</td>
<td>NS</td>
<td>PP</td>
<td>3 g p.o.</td>
<td>10 days</td>
<td>PLT + blood + DDAVP</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
</tr>
<tr>
<td>Fagher et al. (1990) [39]</td>
<td>Sweden</td>
<td>21</td>
<td>Vaginal bleeding</td>
<td>No</td>
<td>Normal</td>
<td>NS</td>
<td>26</td>
<td>4 g i.v. + 4 g p.o.</td>
<td>1 day</td>
<td>Terbutaline + CC</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
</tr>
<tr>
<td>Greer et al. (1991) [30]</td>
<td>UK</td>
<td>NS</td>
<td>Secondary PPH</td>
<td>Hemophilia</td>
<td>NS</td>
<td>NS</td>
<td>PP</td>
<td>NS</td>
<td>1 day</td>
<td>Cryoprecipitates + PLT</td>
<td>No</td>
<td>No</td>
<td>Stopped</td>
</tr>
<tr>
<td>Hahn (1995) [45]</td>
<td>Sweden</td>
<td>35</td>
<td>Coagulopathy due to amphetamine</td>
<td>No</td>
<td>93 × 10^9 L</td>
<td>NS</td>
<td>23</td>
<td>4 g i.v.</td>
<td>1 day</td>
<td>FFP + fibrinogen</td>
<td>No</td>
<td>No</td>
<td>Stopped</td>
</tr>
<tr>
<td>Alok et al. (1996) [27]</td>
<td>UK</td>
<td>39</td>
<td>Secondary PPH due to placenta accreta</td>
<td>No</td>
<td>&gt; 1300</td>
<td>PP</td>
<td>3 g i.v.</td>
<td>1 day</td>
<td>Blood + FFP + collodids + uterotonics</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Good, 3</td>
</tr>
<tr>
<td>Dauleh et al. (1997) [46]</td>
<td>Qatar</td>
<td>36</td>
<td>Hematurnia due to placenta percreta invasion of bladder</td>
<td>No</td>
<td>NS</td>
<td>4500</td>
<td>36</td>
<td>2 g i.v.</td>
<td>1 day</td>
<td>STH + cysctomy + FFP + collodids</td>
<td>No</td>
<td>No</td>
<td>Not stopped Complicated</td>
</tr>
<tr>
<td>Selcuk et al. (2001) [31]</td>
<td>Turkey</td>
<td>26</td>
<td>Secondary PPH</td>
<td>Evans syndrome</td>
<td>49 × 10^9 L</td>
<td>NS</td>
<td>PP &gt; 20 days</td>
<td>NS</td>
<td>1 day</td>
<td>Methylergonovin + blood</td>
<td>No</td>
<td>No</td>
<td>Stopped</td>
</tr>
<tr>
<td>Carradice et al. (2002) [28]</td>
<td>New Zealand</td>
<td>16</td>
<td>Multiple hemorrhagic features</td>
<td>Leukemia</td>
<td>23 × 10^9 L</td>
<td>NS</td>
<td>25</td>
<td>NS</td>
<td>NS</td>
<td>DDAVP + CC + antibiotics</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
</tr>
<tr>
<td>Poutamo et al. (2003) [40]</td>
<td>Finland</td>
<td>21</td>
<td>Vaginal bleeding after termination</td>
<td>No</td>
<td>NS</td>
<td>NS</td>
<td>16</td>
<td>NS</td>
<td>1 day</td>
<td>Misoprostol + intrauterine alcohol tamponade</td>
<td>No</td>
<td>No</td>
<td>Gradually stopped</td>
</tr>
</tbody>
</table>

*Preterm delivery of a growth retarded neonate.
†Massive infection-sepsis the patient was subjected to multiple operations.
§Patient expired.

AFE: Amniotic fluid embolism; CC: Corticosteroids; DDAVP: Desmopresin; FFP: Fresh frozen plasma; i.v.: Intravenous; NS: Not stated; PLT: Platelets; p.o.: per os; PP: Post-partum; PPH: Post-partum hemorrhage; RF: Vila-recombinant factor VIIa; STH: Subtotal abdominal hysterectomy; TA: Tranexamic acid; TAH: Total abdominal hysterectomy.
Table 3. Characteristics of the case reports that reported use of tranexamic acid during pregnancy (continued).

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Age (years)</th>
<th>Indication (symptomatology)</th>
<th>Concomitant disease</th>
<th>PLT count</th>
<th>Blood loss (ml)</th>
<th>Weeks (period)</th>
<th>Dosage of TA</th>
<th>Duration</th>
<th>Additional treatment</th>
<th>Adverse effects</th>
<th>Response</th>
<th>Pregnancy outcome, level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouwmeester et al. (2003) [32]</td>
<td>Netherlands</td>
<td>30</td>
<td>Primary PPH + coagulopathy</td>
<td>Vaginal bleeding due to uterine rupture</td>
<td>No</td>
<td>$135 \times 10^8$</td>
<td>NS</td>
<td>PP</td>
<td>NS</td>
<td>NS</td>
<td>TAH + ligation of iliac arteries + RF-VIIa + FFP</td>
<td>Uterine artery ligation</td>
<td>No</td>
</tr>
<tr>
<td>Gupta et al. (2003) [41]</td>
<td>India</td>
<td>27</td>
<td>Primary PPH due to uterine rupture</td>
<td>No</td>
<td>NS</td>
<td>2000</td>
<td>36</td>
<td>1 g i.v.</td>
<td>1 day</td>
<td>Uterotonics + FFP + blood</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Complicated, 3</td>
</tr>
<tr>
<td>Nagar et al., 2005 [42]</td>
<td>UK</td>
<td>38</td>
<td>Primary PPH and coagulopathy</td>
<td>AFE</td>
<td>$48 \times 10^9$ L</td>
<td>2000</td>
<td>PP</td>
<td>1 g i.v.</td>
<td>3 days</td>
<td>FFP + blood + PLT + uterotonics</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Complicated</td>
</tr>
<tr>
<td>Porteous et al. (2005) [33]</td>
<td>UK</td>
<td>32</td>
<td>Primary PPH</td>
<td>Hemophilia</td>
<td>NS</td>
<td>2600</td>
<td>PP</td>
<td>1 g i.v.</td>
<td>19 days</td>
<td>RF-VIIa + DDAVP + FFP + CC pudendal embolisation</td>
<td>No</td>
<td>Not stopped</td>
<td>Good, 3</td>
</tr>
<tr>
<td>Kopeck et al. (2005) [34]</td>
<td>Poland</td>
<td>24</td>
<td>Secondary PPH</td>
<td>Bernard Soulier s.</td>
<td>$50 \times 10^9$ L PP</td>
<td>NS</td>
<td>PP</td>
<td>NS</td>
<td>NS</td>
<td>DDAVP + uterotonics</td>
<td>No</td>
<td>Stopped</td>
<td>Good, 3</td>
</tr>
<tr>
<td>Kiplani et al. (2005) [35]</td>
<td>India</td>
<td>31</td>
<td>Secondary PPH</td>
<td>Bernard Soulier s.</td>
<td>$47 \times 10^9$ L</td>
<td>&gt; 1500 PP</td>
<td>500 mg i.v.</td>
<td>1 day</td>
<td>Blood + FFP</td>
<td>No</td>
<td>Stopped</td>
<td>Good, 3</td>
<td></td>
</tr>
<tr>
<td>Phabu et al. (2006) [36]</td>
<td>UK</td>
<td>1st 23</td>
<td>Secondary PPH</td>
<td>Bernard Soulier s.</td>
<td>$37 \times 10^9$ L</td>
<td>1000 PP</td>
<td>1 g i.v.</td>
<td>1 day</td>
<td>Blood + FFP + colloid + PLT</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Good, 3</td>
<td></td>
</tr>
<tr>
<td>Rahman et al. (2008) [37]</td>
<td>UK</td>
<td>2nd 37</td>
<td>Secondary PPH</td>
<td>Bernard Soulier s.</td>
<td>$14 \times 10^9$ L</td>
<td>1500 PP</td>
<td>1 g p.o.</td>
<td>1 day</td>
<td>Blood + FFP + colloid + PLT</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Good, 3</td>
<td></td>
</tr>
<tr>
<td>Rahman et al. (2008) [37]</td>
<td>UK</td>
<td>37</td>
<td>Primary PPH due to placenta diffusa</td>
<td>Platelet storage pool disease</td>
<td>Normal</td>
<td>8000 PP</td>
<td>1 g i.v. before delivery</td>
<td>1 day</td>
<td>Hysterectomy + blood + PLT + FFP + oxytocin</td>
<td>No</td>
<td>Not stopped</td>
<td>Complicated, 3</td>
<td></td>
</tr>
<tr>
<td>Nohira et al. (2008) [43]</td>
<td>Japan</td>
<td>33</td>
<td>Vaginal bleeding due to placenta accreta</td>
<td>No</td>
<td>$46 \times 10^9$ L</td>
<td>19000</td>
<td>35</td>
<td>4 g i.v.</td>
<td>3 days</td>
<td>Hysterectomy + blood + RF-VIIa + FFP + PLT</td>
<td>No</td>
<td>Not stopped</td>
<td>Complicated, 3</td>
</tr>
<tr>
<td>Annecke et al. (2010) [26]</td>
<td>Germany</td>
<td>36</td>
<td>Primary PPH and coagulopathy</td>
<td>AFE</td>
<td>$75 \times 10^9$ L</td>
<td>NS</td>
<td>PP</td>
<td>1 g i.v.</td>
<td>1 day</td>
<td>Hysterectomy + blood + FFP + fibrinogen</td>
<td>No</td>
<td>Gradually stopped</td>
<td>Complicated, 3</td>
</tr>
</tbody>
</table>

*Preterm delivery of a growth retarded neonate.

1Massive infection-sepsis the patient was subjected to multiple operations.

2Patient expired.

AFE: Amniotic fluid embolism; CC: Corticosteroids; DDAVP: Desmopresin; FFP: Fresh frozen plasma; i.v.: Intravenous; NS: Not stated; PLT: Platelets; p.o.: per os; PP: Post-partum; PPH: Post-partum hemorrhage; RF: Vila-recombinant factor VIIa; STH: Subtotal abdominal hysterectomy; TA: Tranexamic acid; TAH: Total abdominal hysterectomy.
of gestation managed successfully with tranexamic acid. The patient delivered a healthy baby by cesarean section at 34 weeks. Tranexamic acid was also used in an observational study including 73 consecutive patients with placental abruption with no adverse effects [14].

Tranexamic acid inhibits fibrinolysis and therefore carries a potential risk of thrombosis especially in patients with previous history of thrombosis and in pregnant women. Tranexamic acid has no effect on overall blood coagulation parameters (e.g., platelet counts, activated partial thromboplastin time and prothrombin times), as determined by studies in patients undergoing a variety of surgical procedures [51]. Additionally, in a study by Dockery et al. [22], it was observed that tranexamic acid administration for treatment of menorrhagia resulted in reduction of t-PA (tissue plasminogen activator) and plasmin activity in menstrual and peripheral blood.

The incidence of thrombosis during pregnancy and puerperium is five to six times higher than that in the general population, and postpartum venous thromboembolism is more common than antepartum venous thromboembolism [48]. Pulmonary embolism occurred in 2 of 256 pregnant women who received treatment with tranexamic acid in the study by Lindoff et al. [17]. In one case, pulmonary embolism occurred after 2 weeks of treatment. Similarly, among the control group pulmonary embolism and deep venous thrombosis were reported in one and three women, respectively. The possible involvement of tranexamic acid in the thrombotic episode in this patient could neither be confirmed nor excluded [17]. The authors stated that no correlation was observed between thrombotic complications and tranexamic acid administration (p > 0.16). Faher et al. [39] reported the management of pulmonary embolism with streptokinase infusion in a patient that received tranexamic acid 4 g for 10 days as management of placental abruption. However, tranexamic acid was used without any adverse effects in the study by Bekassy et al. [16] in 45 pregnant patients receiving tranexamic acid 3 g for 15 days. However, caution is required in the interpretation of these results, and prolonged treatment with tranexamic acid should be monitored closely to avoid the risk for thrombosis. tranexamic acid is contraindicated in patients with a history of thromboembolic diseases, and dosage reductions are recommended in patients with renal insufficiency [5,62].

Other minor adverse events with tranexamic acid therapy are uncommon and include nausea or diarrhea, but occasional orthostatic reactions are most often reported. No mutagenic activity of tranexamic acid has been detected in in vitro and in vivo test systems [62,63] and no fetal abnormalities were identified in early dysmorphology and reproductive studies in animals [64,65]. Excretion in breast milk is low: the concentration of tranexamic acid in breast milk of lactating women 1 h after the last dose of 2 days’ treatment was ~ 1% of the peak serum concentration; therefore it can be used safely in lactating women [66].

92 ml (95% CI 76 – 109) compared with no treatment. There was no evidence of heterogeneity between trials (I² = 0%, \( \chi^2 = 1.44, df = 2, p = 0.49 \)). A Cochrane systematic review [61] of two RCTs (one study with vaginal delivery [7] and one with cesarean section [8]) has also concluded that tranexamic acid decreases blood loss after vaginal and cesarean delivery. Blood loss of > 400 ml was less common in women who received tranexamic acid after vaginal birth or cesarean section in the dosage of 1 g or 0.5 g (risk ratio [RR] = 0.51, 95% CI 0.36 – 0.72). Mean blood loss was lower in the group of women who received tranexamic acid (mean difference [MD] -75.17 ml, 95% CI -108.23 to -42.12 ml). Our study is a systematic review of all available reports in the international literature on the use of tranexamic acid during pregnancy and postpartum. We assessed three studies, administrating tranexamic acid before a cesarean section [8,10,11]. Our meta-analysis showed a reduction of 32.5 ml in blood loss in the tranexamic acid group versus placebo (95% CI -4.1 – 69.13; \( p = 0.08 \)). In addition, evidence of significant heterogeneity was observed between the three RCTs (\( p < 0.0001 \)). We must emphasize that the three RCT trials did not have a good methodological quality, based on assessment and grading according to Shulz criteria [5]. The studies did not report blinding and ITT analysis; therefore, it should be considered that the existence of detection and performance biases cannot be excluded from the interpretation of results. In addition, it should be noted that the reduction in blood loss associated with tranexamic acid use for prevention of PPH seems marginal in our and previous systematic reviews [21,61] and its clinical relevance is unknown. A more important measure will be to assess blood transfusion requirements and changes in hemoglobin. Indeed, tranexamic acid was shown in a very recent RCT to reduce blood loss and maternal morbidity (drop in hemoglobin > 4 g/dl and requirement for blood transfusion) when used early for management of women with PPH [13].

In addition, tranexamic acid has also been used successfully to provide a hemostatic cover for obstetric interventions and delivery or to control PPH in women with bleeding disorders such as von Willebrand disease, FXI deficiency, Bernard Soulier syndrome, platelets disorders, etc. Tranexamic acid provides a very useful alternative to blood products for these patients.

Tranexamic acid has been suggested for management of women with early-pregnancy bleeding (threatened miscarriage) to control the bleeding, thus reducing the risk of miscarriage. In a randomized trial by Tetruashvili [12], tranexamic acid use in such women was associated with a reduction in duration of bleeding episode. Similarly, tranexamic acid has also been used for women with antepartum hemorrhage due to placenta abruption or placenta previa [14,15,17,20]. Placental abruption is characterized by activation of the fibrinolytic system [14], and tranexamic acid can offer local hemostasis and reduce risk of premature labor [4]. Asted et al. [38] reported the first case of placental abruption at 26 weeks of gestation managed successfully with tranexamic acid. The patient delivered a healthy baby by cesarean section at 34 weeks. Tranexamic acid was also used in an observational study including 73 consecutive patients with placental abruption with no adverse effects [14].
The optimal dosage and the route of administration in obstetric patients is unknown. In general, according to the manufacturer and clinical investigations for local fibrinolysis, the recommended dosage is 500 mg – 1 g by slow intravenous injection three times daily or 1 – 1.5 g orally two to three times daily. In addition, for general fibrinolysis, a single dose of 1 g or 10 mg/kg by slow intravenous injection is recommended [62].

Walzman et al. [15] suggested that fibrinolytic activity is significantly reduced in pregnancy when tranexamic acid is given in a dosage of 1 g 8 hourly; this dose reduced plasma plasminogen levels thus accelerating hemostasis in uteroplacental circulation in 12 pregnant patients with vaginal bleeding. Hemorrhage due to disseminated intravascular coagulation should not be treated with any antifibrinolytic agent unless both bleeding tendency and systemic fibrinolysis are present [67]. Annecke et al. [26] treated coagulation defects in a catastrophic case of amniotic fluid embolism. Despite the fatal outcome of the patient, the authors halted extensive hyperfibrinolysis via administration of tranexamic acid, platelets and fibrinogen. Coagulation status was evaluated via thrombelastometry. In addition, the authors suggested infusion of tranexamic acid in a dosage of 10 – 20 mg/kg body weight before infusion of fibrinogen and platelets [26].

9. Conclusion

In conclusion, tranexamic acid seems to be an effective treatment for antepartum and postpartum hemorrhage, and several clinical trials have highlighted its use in reducing postpartum blood loss and transfusion requirements. No significant maternal and neonatal complications were noted after its use. It also has a good tolerability profile and no teratogenic effects in fetuses. Larger clinical trials and further investigation in the pregnant population are required to reach more definite conclusions.

An international trial, WOMAN (world maternal antifibrinolytic trial), has now been established to determine the effect of early administration of tranexamic acid on mortality, hysterectomy and other morbidities (surgical interventions, blood transfusion, risk of nonfatal vascular events) in women with clinically diagnosed postpartum hemorrhage. The treatment will entail a dose of tranexamic acid (1 g i.v.) or placebo (sodium chloride 0.9%) administered as soon as possible after randomization. A second dose may be given if, after 30 min, bleeding continues, or if the bleeding stops and restarts within 24 h after the first dose [9]. Information regarding the design and randomization of the trial can be obtained at http://www.womantrial.lshtm.ac.uk.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
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Affiliation

Panagiotis Peitsidis MD PhD & Reza Kadar MD MRCOG FRCOG(Ed) MD

Author for correspondence

The Royal Free Hospital, Haemophilia Centre & Thrombosis Unit, Department of Obstetrics and Gynaecology, Pond Street, NW3 2QG London, UK

E-mail: panagiotis_pp@yahoo.com