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Review article

Therapeutic plasma exchange in pregnancy: A literature review

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ABSTRACT

Therapeutic plasma exchange (TPE) is indicated as a treatment for a wide array of diseases, extensively addressed in the Guidelines of the American Society for Apheresis. In pregnancy, TPE is an uncommon event and application is largely based on extrapolation of efficacy and safety in a non-pregnant population. This review intends to describe the currently available experience of TPE in pregnancy to help clinicians recognise indications during pregnancy and to support current guideline recommendations with literature-based experiences. In order to identify the clinical indications for which TPE is applied in pregnant women, we performed a literature search including studies till November 2019, without a start date restriction. Data extraction included medical indication for TPE and safety of TPE in pregnant women. 279 studies were included for analysis. Nowadays, TPE is predominantly applied for thrombotic microangiopathies, lipid disorders and a variety of autoimmune diseases. The application of TPE during pregnancy remains largely empiric and relies on individual case reports in the absence of high-quality studies and definitive evidence-based guidelines. Safety profile of TPE during pregnancy appears to be comparable to application of TPE in non-pregnant patients. In conclusion, based on the limited evidence that we found in literature with a high risk of publication bias, TPE procedures can be used safely during pregnancy with the appropriate preparation and experience of a multidisciplinary team.

Contents

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Introduction

Therapeutic plasma exchange (TPE), the most broadly adapted apheresis technique, is an extracorporeal treatment which focuses on removal of soluble components from plasma. The purpose of TPE is reduction of a pathogenic substance or correction of plasma proteins. In TPE, blood of the patient passes through a medical device which separates plasma from other components of blood, which can then be removed and reinfused with the addition of a replacement fluid, such as albumin, saline 0.9 % or plasma [1]. Various apheresis procedures are used for a wide array of clinical indications in non-pregnant patients. The 8th edition of the American Society for Apheresis (ASFA) guidelines provides clear definitions for the different apheresis procedures and their therapeutic indications [1].

Since many of the diseases listed in the ASFA guidelines can also be present in pregnancy, they state in their guidelines that apheresis can be performed safely during pregnancy, while warning for potential side effects such as hypotension which theoretically can result in decreased placental perfusion and fetal oxygenation [1–5]. Also, important physiological changes during pregnancy, such as increased circulating blood volume, haemodilution, increased cardiac output, and potentially increased risk of infections, should be kept in mind when performing apheresis procedures in pregnant women [2]. Furthermore, from a pathophysiological point of view, TPE may also be of benefit for pregnancy-specific diseases as pharmacological treatments during pregnancy are often hampered by potential fetal toxicity.

It is important to realize that the rationale for employing TPE in pregnant women is predominantly based on pathophysiological thinking (rather than evidence-based), on the premise that the removal of a pathogenic substance has the potential to benefit mother and the unborn child. Moreover, there is a high threshold for treating physicians to initiate TPE in a pregnant woman, likely because TPE in pregnancy is rare in addition to the lack of high quality, evidence-based studies on the efficacy and safety of TPE in pregnancy.

Therefore, we performed a literature review to provide an overview of potential safety issues to which treating physicians can anticipate to and a literature-based framework on the most commonly reported indications for TPE in pregnancy. Since the first report of TPE in pregnancy in 1968, TPE techniques have significantly improved, our knowledge on the pathophysiology of many diseases has expanded, and TPE has gained a more established place in the physician's therapeutic armamentarium for maternal disease during pregnancy [1,2,6,7].

Methods

In order to identify the clinical indications for which TPE is applied in pregnant women, we performed a literature search using a search strategy including the terms "blood component removal", "apheresis", "plasma exchange", and "plasmapheresis" combined with keywords for pregnancy (detailed search strategy in supplemental file). The search included studies published till November 2019 in PubMed, Embase, Web of Science and Cochrane library, without a start date restriction. Conference abstracts and studies in other languages than English were excluded. Because the present review focuses on apheresis procedures that remove soluble components, we excluded studies describing cell-separating apheresis procedures (i.e. adsorptive cytapheresis, erythrocytapheresis, red blood cell exchange, thrombocytapheresis, leukocytapheresis, and rheopheresis). No limit was placed on quality of any article. However, studies without full-text availability, missing data on the numbers treated, or clinical indication, had to be excluded.

In order to estimate reported complications of TPE in pregnancy, data extraction from each individual study was performed by 3 investigators independently. Duplicate studies or overlap in patients reported from the same cohort or institution were identified, in which case only the most recent or larger cohort paper was selected. Data on any reported complications was collected and accumulated. Descriptive statistics were used to summarize the frequency (%) of reported side effects.

Results

Importantly, we found no clinical trials specific to pregnant women on the use of TPE, which supported our previously mentioned premise that pregnant women are treated based upon extrapolating data from studies in the non-pregnant population. We included 279 studies for analysis of which 239 case reports/series, 24 retrospective and 16 prospective cohorts (Fig. 1). The most reported clinical conditions for which TPE was applied in pregnant women were summarized in Table 1. We included the grade of recommendation for the use of TPE in each clinical condition, extracted from the most recent 8th edition of the ASFA guidelines [1]. It is noteworthy to recognise that, in 8/15 (53 %) indications reported in pregnant women TPE was strongly recommended for non-pregnant patients. Vice versa, in 7/15 (47 %) indications TPE was only weakly recommended with moderate to very low-quality evidence supporting its application. Below, we provide a more in-depth description of safety issues and reported indications for TPE, which were summarized in Fig. 2.

Safety issues

Safety issues identified from the literature review

Table 2 summarizes the results of our data extraction of all selected studies resulting in a calculated frequency and incidence of side effects and complications of TPE in pregnant women. For comparison we illustrated, the occurrence of these identical side effects as summarized in a study on >15.000 procedures for non-pregnant patients [8]. As such, in the non-pregnant population, the most common side effects of TPE include: urticaria (0.7–12.0%) or rigors (1.1–8.8%) from transfusion-related allergic reactions, perioral and digital paraesthesia due to hypocalcaemia (1.5–9.0%), hypotension (0.4–4.2%), and headaches (0.3–5.0%) or muscle cramps (0.4–2.5%) caused by hypovolemia [5,8]. The number of side effects in pregnancy found in literature shows that the incidence of hypotension is higher (5.2 %), while all other complications are either equal or less than in the non-pregnant population. One of the largest cohorts included, performed apheresis procedures in 57 pregnancies in a single centre and had 20 (2.1 %) adverse events during 13.251 sessions, of which 65 % technical problems, and none required prolongation of hospitalization [3].

Potential safety issues in pregnant patients based on pathophysiology

The most reported and important side effect of TPE in pregnancy is the maternal blood pressure drop during the procedures [3,5,9–12]. Fetal distress in the form of change in heart beat frequency has been described in four studies (1.1 % of pregnancies); all in relation to maternal hypotension during TPE, and all were transient after saline infusion [9,13–15]. Therefore, maintaining an adequate maternal intravascular volume by saline infusions during TPE is essential and, in the second or third trimester, the patient should lay on her left side to avoid compression of the inferior vena cava by the gravid uterus [1]. In a substantial amount of studies the safety on placental blood flow was maintained by frequent umbilical doppler measurements and fetal cardiotocography in between or during apheresis

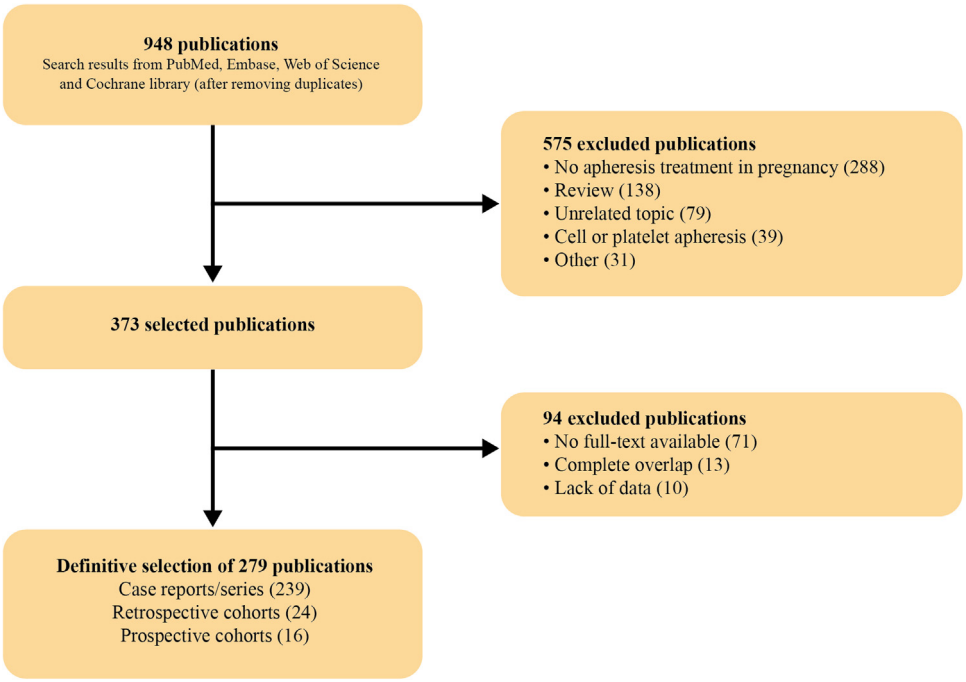

Fig. 1. Flowchart of included publications for the literature review.

Table 1
Reported studies categorised by their indications for apheresis in pregnancy.

	Stated by ASFA guidelines (8th edition)			Reported in literature			
Indication for apheresis in pregnancy	Type of apheresis	Category*	Grade*	Case reports/ series (n)	Retrospective cohorts (n)	Prospective cohorts (n)	Total studies (n)
Obstetric							
Red cell alloimmunization	TPE	III¶	2C¶	44 (103)	4 (29)	7 (168)	55 (300)
Thrombotic microangiopathy				*Pregnant patients*			
HELLP syndrome	TPE	Postpartum:	2C	24 (34)	4 (56)	2 (39)	30 (129)
		III	2C	2 (2)	–	–	2 (2)
		Antepartum: IV					
Thrombotic thrombocytopenic purpura	TPE	I	1A	44 (66)	6 (40)	1 (2)	51 (108)
(Catastrophic) antiphospholipid syndrome	TPE/IA	I	2C	10 (22)	3 (34)	2 (24)	15 (80)
Pre-eclampsia	TPE/LA/sFlt-1 apheresis	n.a.β	n.a.β	4 (10)	–	4 (34)	8 (44)
Hemolytic Uremic Syndrome	TPE	III	2C	6 (6)	–	–	6 (6)
Autoimmune	*Non-pregnant patients*			*Pregnant patients*			
Congenital Heart Block (CHB)/ Cardiac neonatal lupus	TPE/IA	III	2C	8 (12)	3 (27)	–	11 (39)
Multiple Sclerosis	TPE/IA	II	1A/B	4 (4)	2 (21)	–	6 (25)
Systemic Lupus Erythematosus (SLE)	TPE	II	2C	5 (5)	3 (11)	–	8 (16)
Polyneuropathy (Guillain-Barré Syndrome)	TPE/IA	I	1A/B	7 (8)	1 (4)	–	8 (12)
Myasthenia Gravis	TPE	I	1B	7 (8)	1 (3)	–	8 (11)
Neuromyelitis optica	TPE	II	1B	4 (9)	–	–	4 (9)
Pemphigus vulgaris	TPE/IA	III	2B	6 (6)	–	–	6 (6)
Metabolic	*Non-pregnant patients*			*Pregnant patients*			
Hypertriglyceridemic pancreatitis	TPE/LA	III	1C	21 (25)	4 (42)	–	25 (67)
Familial hypercholesterolemia	LA	I	1A	11 (16)	–	–	11 (16)
	TPE	II	1B	2 (12)	–	–	2 (12)

Categorized indications for apheresis in pregnancy: obstetric, thrombotic microangiopathy, autoimmune, and metabolic. Category and Grade recommendations according to ASFA guidelines 2019 for non-pregnant patients and the number of studies found in medical literature where apheresis is applied in pregnancy, divided in subgroups: case reports/series, retrospective and prospective cohorts with the number (n) of pregnancies treated. Abbreviations: TPE, Therapeutic plasma exchange; LA, Lipoprotein apheresis; IA, Immunoadsorption.
Category I: disorders for which apheresis is accepted as first line therapy; Category II: disorders for which apheresis is accepted as 2nd line therapy; Category III: optimum role of apheresis therapy is not established; Category IV: disorders in which published evidence demonstrates or suggest apheresis to be ineffective or harmful.
Grade 1A: strong recommendation, high quality evidence; Grade 1B: strong recommendation, moderate quality evidence; Grade 1C: strong recommendation, low or very low quality evidence; Grade 2A: weak recommendation, high quality evidence; Grade 2B: weak recommendation, moderate quality evidence; Grade 2C: weak recommendation, low or very low quality evidence.
* As stated by ASFA guidelines for non-pregnant patients.
¶ Prior to intravascular intrauterine transfusion (IUT) availability.
β No fact sheet listed on this topic in the ASFA guidelines.

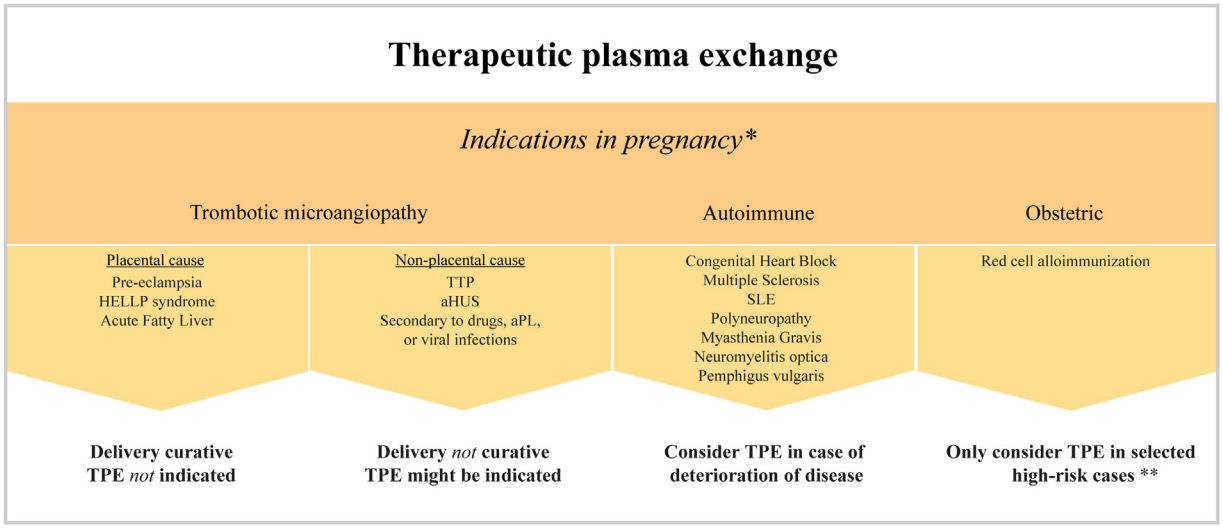

Fig. 2. Overview of indications for therapeutic plasma exchange in pregnancy.

Table 2
Side effects and complications of apheresis in pregnant and non-pregnant patients.

Category	Symptoms	Reported in the non-pregnant population (%) *	Reported in pregnancy (%) ¶ N = 753 pregnancies	Number of studies reporting side effect	Design of reporting studies
Hypovolemia	Hypotension	0.4–4.2	39 (5.2)	12	6 CR, 2 RC, 4 PC
	Muscle cramps	0.4–2.5	2 (0.3)	1	1 RC
	Nausea	0.1–1.0	4 (0.5)	3	2 CR, 1 PC
	Headaches	0.3–5.0	5 (0.7)	3	3 CR
Anaphylactic	Urticaria	0.7–12.0	22 (2.9)	8	6 CR, 2 RC
	Rigors	1.1–8.8	0	0	0
Obstetric	Fetal distress β	–	8 (1.1)	4	3 CR, 1 PC
	Neonatal infection	–	0	0	0
	Ante- or postpartum hemorrhage	–	2 (0.3)	2	2 CR
Hypocalcemia	Paresthesia	1.5–9.0	8 (1.1)	6	5 CR, 1 RC
Pulmonary	Respiratory arrest/pulmonary edema	0.2–0.3	5 (0.7)	2	2 CR
	Pulmonary embolism	0.1	0	0	0
	Pneumothorax	0.1	1 (0.1)	1	1 CR
Hematologic	Thrombosis/hemorrhage	0.02–0.70	4 (0.5)	4	1 CR, 1 RC, 2 PC
Infectious	Hepatitis	0.7	3 (0.4)	1	1 CR
	Access related	0.3	3 (0.4)	3	3 CR
Cardiac	Myocardial ischemia/ infarction/shock	0.1–1.5	0	0	0
	Arrhythmia	0.1–0.7	0	0	0
Neurologic	Seizures	0.03–0.40	0	0	0
	Cerebrovascular ischemia	0.03–0.10	0	0	0
Pyrogenic	Hyperthermia	0.7–1.0	0	0	0

CR = case report/series, RC = retrospective cohort, PC = prospective cohort.
* Occurrence of specific side or adverse effects attributed to therapeutic apheresis in pregnant patients included in Table I (% of 753 total pregnancies), postpartum HELLP excluded.
¶ Incidence percentages of adverse events for non-pregnant patients were adapted from Kaplan, A. *Complications of apheresis.* Semin Dial, 2012. 25(2): p. 152–8. Data from multiple references comprising over 15.000 treatments. [8].
β Signs of fetal distress defined as change in fetal heartbeat frequency or ultrasound/doppler during or shortly after therapeutic apheresis.

sessions. Of interest, no adverse effect on fetal dopplers or cardiotocography were reported, suggesting that fetal circulation is uncompromised during TPE procedures when maternal intravascular volume is warranted. It is, therefore, matter of debate whether cardiotocography and/or ultrasound assessments are necessary during TPE procedures, and whether local practices can support the logistic challenges of performing TPE and cardiotocography simultaneously [10,10,11,12,16,17].

The most common adverse event associated with plasma replacement is an allergic reaction where the risk for a single unit of fresh frozen plasma (FFP) is 1.4 % [5]. Allergic reactions were reported in 2.9 % of pregnancies, all when FFP was used as a replacement fluid. The use of albumin or saline as a replacement fluid in TPE reduces the frequency of allergic reactions, although these fluids are associated with other side effects such as depletional coagulopathy, which is not seen if FFP is used [5].

When employing TPE, one needs to realize that besides the removal of potential pathogenic components, also coagulation factors, drug altering enzymes, and immunoglobulins are extracted from the maternal blood. In one volume exchange session, coagulant proteins and immunoglobulins decrease 30–50 % from their baseline levels. Therefore, based on these pathophysiological concepts, increased risks on postpartum haemorrhage can be mitigated by monitoring fibrinogen levels near onset of labour and to leave an interval of at least 24 h, depending on the clinical situation, between the last TPE session and a (planned) delivery [2,18]. In order to estimate the chance on potential neonatal infections, determination of immunoglobulin levels of the newborn can be considered [2]. Also, re-administration of prophylactic RhIg may be considered if TPE is performed in the third trimester [18]. In addition, when applying general anaesthesia after TPE in pregnancy, there is a possible depletion of drug altering enzymes such as cholinesterase, which could lead to prolonged paralysis after succinylcholine administration [19,20].

Symptoms due to hypocalcaemia, could be overcome by monitoring calcium levels prior to the procedure and prophylactic administration if necessary, orally or intravenously [18].

Another important issue when employing TPE in pregnant women concerns the estimation of blood and plasma volume in pregnant women and henceforth a underestimation of plasma volume exchanged during TPE procedures, which could potentially lead to a reduced efficacy of the treatment and maternal hypotension [18]. Therefore, several approaches attempt to adjust for the plasma expansion, i.e. using the pre-pregnancy weight, ideal body weight, increasing the calculated plasma volume by a certain factor (e.g. increase the calculated plasma volume in the second and third trimester by 50 %) to ensure that a sufficient volume of 1–1,5 total plasma volumes is exchanged or using the current weight with the assumption that the added weight of the pregnancy itself will compensate for the expanded blood and plasma volume [3,18]. Despite these considerations, the duration and feasibility of a TPE procedure in a pregnant patient is foremost dependent on how well the procedure can be tolerated.

Lastly, most of the apheresis procedures can be performed using a venous catheter of the forearm as blood access point, but when a prolonged treatment time is expected or peripheral venous access is difficult, a tunnelled internal catheter is indicated. The insertion of a rather large intravenous catheter can lead to bleeding, lung puncture (depending on the site of catheter insertion), thrombosis, and has a higher chance of getting infected. Total access complications account for about 1% of all adverse events in the general population, which is comparable when performed in pregnancy (Table 2) [5,21,22].

Overview of commonly reported indications for TPE in pregnancy

TPE in red cell alloimmunization

Red cell alloimmunization (RCA) is a condition in which maternal antibodies directed against fetal red cell antigens lead to hemolytic disease of the fetus and newborn. Fetal anemia can eventually lead to fetal hydrops and death. TPE was applied during pregnancy for the first time in 1968 in a patient with RCA to remove maternal antibodies directed against fetal red cell antigens, and TPE became a common procedure as a preventive strategy in early pregnancy, however, its efficacy has remained uncertain [1,2,7,23,24]. Nowadays, the incidence of hemolytic disease of the fetus and newborn secondary to anti-D is significantly reduced due to prophylactic administration of RhD immunoglobulins, and ultrasound-guided intravascular intrauterine transfusions have now become the standard of care [25–28]. Currently, TPE may only be considered combined with intravenous immunoglobulins (IVIG) in selected high-risk cases with a history or signs of severe fetal anemia before 20 weeks of gestation in order to postpone the moment of the first intravascular intrauterine transfusion [1,27–33]. Since the successful introduction of intravascular intrauterine transfusions in the treatment of fetal anaemia, one of the most prevalent indications for TPE during pregnancy has minimalized.

TPE in thrombotic microangiopathies

Thrombotic microangiopathy (TMA) is a clinical syndrome typically characterized by Coombs-negative haemolysis and low platelet counts. The underpinning pathogenesis of TMA in pregnancy can vary and therefore TMA encompasses a category of disorders with comparable presentation. In the majority of cases, placental ischemia may be the initiating event, leading to production of soluble factor(s) by placental tissue that result in maternal endothelial dysfunction, and thus pre-eclampsia [34]. For these placenta-related causes of TMA, delivery is the only curative treatment.

Consequently, TPE is usually *not* indicated prior to delivery. However, in rare cases, TMA is caused by diseases unrelated to the placenta i.e. thrombotic thrombocytopenic purpura (TTP), atypical haemolytic uremic syndrome (aHUS) or acquired TMA secondary to drugs, antiphospholipid autoantibodies, or viral infections. In these cases, delivery is often indicated due to the clinical presentation of progressive pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) or acute fatty liver of pregnancy, however *not* curative in contrary to placenta-related TMA. In non-placental related causes of TMA, addition and/or continuation of TPE may be indicated and sometimes life-saving [35,36].

Therefore, the suspicion and identification of non-placental causes, such as TTP and aHUS, for TMA in pregnant women, generally mimicking hypertensive and/or pre-eclamptic symptoms, is highly relevant [36]. Pregnancy is estimated to account for the presenting episode of TTP in 10–25 % and the risk of relapse of TTP in pregnancy is between 60 and 90 % [37]. TPE is the first line treatment and should be started as soon as possible to remove anti-ADAMTS-13 autoantibodies as well as replenish ADAMTS-13 [38]. Although in TTP and aHUS similar clinical manifestation and laboratory findings can be found, from a clinical point of view neurologic symptoms are more common in TTP patients, while renal insufficiency is more often seen in aHUS patients [6,39]. The gestational age at which TMA presents during pregnancy can help: aHUS usually presents in the late third trimester or postpartum period, while TTP mostly (but not exclusively) presents earlier [35,36]. Moreover, TTP and aHUS can be discriminated by confirming low ADAMTS-13 activity levels of <10 % in TTP. Subsequently, therapeutic management of pregnant women can be tailored: TPE is first-line treatment for TTP with addition of immunosuppression such as high dose corticosteroids, while for aHUS potent inhibition of complement activation with eculizumab should be considered as an additional therapeutic strategy to TPE in order to overcome the continuous need for TPE and potentially improve renal recovery [1,35].

TMA can also occur secondary to antiphospholipid syndrome (APS) [40]. Current treatments during pregnancy for APS patients include aspirin and heparin to prevent thromboembolic complications [41,42]. It seems, only in those cases of Catastrophic APS (CAPS) during pregnancy, TPE is a potential treatment option when conventional treatment with anticoagulation, steroids and/or IVIG fail. In non-pregnant CAPS patients, TPE as a 2nd line therapy has been associated with improved survival [1,43]. In this respect, it is of interest that the application of TPE has also been reported in women with high-risk APS to prevent pregnancy loss [3,10,16,44].

As the cause of TMA cannot always be discriminated early and rapidly, several studies have attempted to evaluate TPE in

pre-eclamptic women. A recent open pilot study evaluated the safety and potential efficacy of a plasma-specific dextran sulphate column to remove circulating soluble FMS-like tyrosine kinase-1 (sFlt-1) in 11 pregnant women with very preterm pre-eclampsia. [17] This study showed promising results on the prolongation of pregnancy while stabilizing sFlt-1 levels, reducing proteinuria and improving postnatal condition of the neonates [17]. However, other studies showed less favourable and inconsistent results [14,21,45,46]. Subsequently, several case reports have reported a possible clinical benefit of TPE in severe *postpartum* HELLP. One has to consider that many studies lacked investigations, such as ADAMTS-13 measurements to discriminate between placental and non-placental causes of TMA that is associated with the clinical HELLP syndrome [1,47,48]. As such, the ASFA guidelines state that there is no role for TPE in ante-partum HELLP as treatment may delay delivery, the curative treatment for pre-eclampsia and HELLP. If however, maternal condition deteriorates postpartum, application of TPE should be considered, usually until platelet counts are $>100 \times 109$/L or LDH has normalized and additional investigations should be initiated to identify non-placental causes [1,49–53].

Taken together, as differentiation between pre-eclampsia, TTP or aHUS often takes time and is notoriously difficult, TPE should be initiated at the acute presentation after adequate laboratory tests are secured whenever TTP or aHUS are considered. Additionally, if there is any evidence of threatened maternal or fetal condition, delivery should be expedited [36,54].

TPE in autoimmune diseases

TPE is also applied for different maternal autoimmune diseases during pregnancy, on the premise of removing autoantibodies (Table 1). The most common indication is congenital heart block (CHB) associated with neonatal lupus. Currently, no well-established treatment of CHB exist, while hydroxychloroquine use is associated with a reduced incidence of CHB in mothers with a previous pregnancy complicated with CHB [55]. With respect to TPE, the promising outcome of 10 infants with CHB have been reported from mothers treated with the combination of TPE, betamethasone and IVIG during pregnancy. This aggressive combination treatment approach is based on the assumed autoantibody-mediated pathophysiology of CHB attempting to remove the autoantibodies quickly and rigorously. Consequently, a significant decrease of anti-SSa/b autoantibody levels is observed, significant recovery of 2nd degree blocks, increase in heart rate at birth and significantly lower prevalence of pacing in the first year of life. These result are remarkably positive and clinically relevant when compared to the outcomes of 24 CHB patients treated with conventional steroids only [16,56]. Although evidence is limited to a few case reports for pregnant patients with Guillain-Barré syndrome; Myasthenia Gravis; Systemic Lupus Erythematosus; Multiple Sclerosis or Neuromyelitis Optica, TPE is stated as an accepted first or second line treatment in the non-pregnant population [1]. It is arguable that, if no alternative treatment possible, preconceptionally started TPE should be continued in pregnancy for these indications, and in case of deterioration of disease in pregnancy TPE may be taken into consideration [3,57–59].

Therapeutic apheresis in metabolic diseases

Lipid disorders are reported as the sole metabolic disease where therapeutic apheresis has been applied in pregnancy. The pharmacological options for these disorders are largely contra-indicated in pregnancy due to potential teratogenicity [60]. Lipoprotein apheresis (LA) is currently the most effective therapy to control LDL-C levels during pregnancy [1,9,61]. In homozygous familial hypercholesterolemia and hypertriglyceridemic pancreatitis, several publications showed that LA treatment during pregnancy resulted in favourable outcomes [9,11,62,63]. Therefore, LA should be initiated before and continued throughout pregnancy with a frequency that maintains acceptable LDL-C levels for individual patients where patients' tolerability is challenged by the high frequency and length of the LA treatment [9,61]. In addition, LA should be recommended as a 2nd line therapy in pregnant women presenting with acute pancreatitis in association with high levels of triglycerides.

Discussion

It can be concluded that the application of TPE during pregnancy remains largely empiric and relies on individual case reports in the absence of high-quality studies and definitive evidence-based guidelines. No distinct safety issues related to TPE have been reported in pregnant women compared to the general population treated with TPE. While performing this review, we noticed that the main indications for TPE during pregnancy have shifted over time. Therefore, in this review, safety issues and thrombotic microangiopathies are discussed extensively, while addressing other indications more briefly.

This overview of the available reported clinical conditions where TPE has been applied during or around pregnancy demonstrate that, nowadays, indications for apheresis during pregnancy can consist of chronic lipid disorders with uncontrollable levels of LDL or triglycerides when pharmacological therapy is withdrawn in the preconception period; autoimmune disease for which no other safe or effective treatment in the pregnancy setting is available; and a prophylactic and last resort setting for patients with CHB and (C)APS. In case of TMAs presenting during pregnancy, delivery is expedited, while the decision to apply TPE should be based on differential diagnosis (Fig. 2) and maternal conditions postpartum.

Although hypotension is described more often during TPE in pregnancy than in the non-pregnant population, other safety issues of TPE in pregnancy seem to have a favourable profile. However, it is important to note that one should be careful to conclude that the current data in this review reflect the 'true' safety of TPE because obvious reporter bias may be present in the literature reviewed for this study. Additionally, when investigating reported side effects, it needs to be taken into account that published cases are mostly from centres with an experienced team and a controlled setting. Hence, TPE procedures have been reported to be applied safely throughout the entire course of pregnancies to treat acute or chronic maternal conditions and to prevent fetal morbidity, including prolongation of pregnancy to reduce fetal prematurity. Additionally, TPE can sometimes avoid or replace the administration of potentially teratogenic drugs.

The present study can support the counselling of patients on the risks and benefits of TPE in pregnancy. It is important to note that all available knowledge regarding TPE during pregnancy is limited to case series and a few cohort studies. This lack of data is also related to the scarcity of the diseases and the fact that many TPE indications have a low evidence level in the ASFA guidelines. Thus, recommendations will be mostly based on extrapolation of data from studies performed in a non-pregnant population. Given the little evidence available on TPE in pregnancy, it is recommendable to monitor the indications, safety and efficacy in an international registry with predefined key data collection, which might provide better understanding with a higher level of evidence in the future. Overall, based on the limited evidence that we found in literature, TPE procedures can be used safely during pregnancy with the appropriate preparation and experience of a multidisciplinary team.

Ethics

Not applicable.

Contribution to Authorship

All authors contributed to the conception and design of the work. M. Wind: Collected and interpreted the data, wrote the manuscript. YKOT/MS: Conceived the idea for the article, supervised and revised the manuscript for important intellectual content. TJR, AGAG, LEMO, JMML: revised the manuscript for important intellectual content. All authors revised and approved the final draft of the manuscript.

Declaration of Competing Interest

The author reports no conflicts of interest in this work.

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