Congenital and acquired Thrombotic Thrombocytopenic Purpura and Pregnancy: presentation, management and outcome of subsequent pregnancies.

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Running Title: TTP and pregnancy-diagnosis and management

Key words: Pregnancy, TTP, diagnosis, congenital, plasma therapy
KEY POINTS

- In a woman presenting with an initial diagnosis of TTP during pregnancy, congenital TTP was more common than acquired TTP

- Active monitoring and management during pregnancy, results in positive pregnancy outcomes.

ABSTRACT

Pregnancy can precipitate TTP. We present a prospective study of TTP cases from the UK TTP registry with clinical and laboratory data from the largest cohort of pregnancy-associated TTP and describe management through pregnancy, averting fetal loss and maternal complications. 35 women presented with a first TTP episode during pregnancy: 23/47 with their first congenital TTP episode and 12/47 with acute acquired TTP in pregnancy. TTP presented primarily in the 3rd trimester/postpartum but fetal loss was highest in the 2nd trimester. Fetal loss occurred in 16/38 pregnancies before congenital TTP was diagnosed, but in none of the 15 subsequent managed pregnancies. 17/23 congenital cases had a missense mutation, C3178T, within exon 24 (R1060W). There were eight novel mutations. In acquired TTP presentations, fetal loss occurred in 5/18 pregnancies and 2 terminations due to disease. We also present data on 12 women with a history of non-pregnancy-associated TTP: 18 subsequent pregnancies have been successfully managed, guided by ADAMTS13 levels. Congenital TTP presents more frequently than acquired TTP during pregnancy and must be differentiated by ADAMTS13 analysis. Careful diagnosis, monitoring and treatment in congenital and acquired TTP have assisted in excellent pregnancy outcomes.
Introduction

Thrombotic thrombocytopenic purpura (TTP) is an acute, rare, potentially life threatening disorder, presenting with thrombocytopenia, haemolytic anaemia and clinical consequences of microvascular thrombosis, caused by deficiency of ADAMTS13. The majority of acute cases are acquired, auto-antibody mediated, characterised by low ADAMTS13 activity (<10%) and the presence of anti-ADAMTS13 IgG antibodies. A small proportion of TTP cases are due to congenital disease, with low ADAMTS13 activity (<10%), no detectable antibody, confirmed by mutational analyses. Congenital TTP classically presents in neonates and children but diagnosis in adulthood is described, such as pregnancy. In the South East (SE) England registry, 5% of more than 200 TTP episodes (congenital and acquired), occurred relating to pregnancy.

The median age of acute TTP presentation is the 3rd-4th decade, typically affecting women. At least half of all acute episodes of TTP are in women of childbearing age. It is also recognised that pregnancy may be the initial, delayed, presentation of congenital disease. There is limited data differentiating between TTP subtypes presenting in pregnancy and fetal and maternal outcomes in the index and subsequent pregnancies. Similarly, there is a paucity of data around the outcomes of pregnancy in women with a previous remote episode of acquired TTP.

Here we present the largest cohort of women with congenital and acquired TTP relating to pregnancy. In the congenital TTP patients-it represents their first TTP episode. The outcomes of TTP in pregnancy and the management of subsequent pregnancies in women with a history of acute TTP are also presented.

Methods

Cases were identified through referral to a single reference centre (UCL) for laboratory diagnosis of TTP and recruited to the UK TTP registry from January 2009 to January 2013 (MREC 08/H0810/54). 8 cases were referred prior to the registry. Previous documentation relating to some of these cases has been published. Congenital cases presented with thrombocytopenia and MAHA and ADAMTS13 activity <10% with no evidence of an anti-ADAMTS13 autoantibody. ADAMTS13
activity was repeated and upon confirmation of these results, mutational analysis was undertaken. Cases were divided into presentation of TTP before 20 weeks gestation, between 20-29 weeks gestation and from 30 weeks to 6 weeks postpartum. Spontaneous miscarriages, <12 weeks gestation, and termination of pregnancy, not clearly related to an acute TTP episode, were not included in the final numbers of the cohort presented. Furthermore, we present pregnancy outcome in women with previous TTP episodes unrelated to pregnancy. Approval was obtained from an institutional review board for this study (MREC 08/H0810/54). Informed consent was provided according to the Declaration of Helsinki.

Management of TTP presenting in pregnancy

Patients were managed according to the protocol in Figure 1.

Prior to 2009, subsequent pregnancies in women diagnosed with congenital TTP, were managed with PEX every 2 weeks from positive pregnancy test. If there was a reduction in platelet count to <150x10^9/L, the frequency of PEX was increased to weekly until delivery. Women also received postpartum PEX, usually immediately after delivery and monitored for at least 6 weeks.

Since 2009, patients have been managed with plasma infusion from 8-10 weeks gestation, initially every 2 weeks, increasing to weekly from the 2<sup>nd</sup>/early 3<sup>rd</sup> trimester or if the platelet count drops below 150 x 10^9/L or increasing LDH. All patients received Octaplas (Octapharma, UK) as plasma replacement.

ADAMTS13 assays

ADAMTS13 activity was determined by measuring the residual collagen binding activity of degraded exogenous VWF until 2010, when analysis has been using the Fluorescence Resonance Energy Transfer (FRETS) assay (normal range: 60-123%). Anti-ADAMTS13 IgG antibodies were measured using an in house ELISA.
Genomic DNA was extracted from whole blood using an in house ammonium chloride/DTAB/ethanol precipitation method. (Sigma Aldrich, Dorset UK). The 29 exons (and intronic boundaries) of \textit{ADAMTS13} were amplified using PCR with Biotaq DNA polymerase, 10×NH$_4$ buffer, 50mM MgCl$_2$ solution and 10mM dNTP mix (Bioline, London UK). The oligonucleotide primers (Invitrogen, Paisley, UK) and PCR conditions used are available on request. NG_011934.1 was used as the genomic DNA reference sequence; NM_139025.3 was used as the cDNA reference sequence. Amplification products were cleaned using Qiagen.

Role of the funding Source:

The UK TTP registry was supported by a grant from the Medical Research Council from 1$^{st}$ January  2009 for 4 years. It provided funding for scientific and data support, capturing all cases of TTP in the UK. Included are a unique dataset, admission and remission samples and a DNA biobank.

Results:

Forty-seven women who had 91 pregnancies are included. 35 women presented with \textit{de novo} TTP in pregnancy. Twenty-three women had late onset congenital TTP (cTTP) with no previous episodes of TTP before their presentation in pregnancy and twelve women had acquired antibody mediated TTP presenting for the first time in pregnancy. The remaining 12 women had suffered a previous episode of acute TTP unrelated to pregnancy and subsequently became pregnant.

A. Congenital TTP presenting in pregnancy (n=23)

There were fifty-three pregnancies, including previous pregnancies before TTP was considered, the index pregnancy when TTP was diagnosed and management of pregnancies following diagnosis of cTTP (Table 1).

cTTP was diagnosed in 20 women following \textit{de novo} presentation in pregnancy. Two women had pregnancies affected by TTP but were diagnosed with cTTP later in
life. The final case (case 18) had a diagnosis of cTTP made as part of family screening of her siblings with poor obstetric outcomes and acute TTP in pregnancy. Therefore, she had an actively managed index pregnancy.

Pregnancies in women with congenital TTP preceding the diagnosis

Eighteen pregnancies preceded the diagnosis of cTTP. None of these pregnancies presented less than 20 weeks gestation. Between 20-29 weeks gestation there were 10 pregnancies in 7 women resulting in 2 live births (both at 27 weeks gestation), and 8 in utero fetal deaths (IUFD’s). In presentations after 30 weeks gestation, there were 8 pregnancies in 4 women of which 5 resulted in live births (including one set of twins) and 3 resulted in IUFD (including one set of twins).

Outcome of the index pregnancy in which cTTP presented

Three women, presenting before 20 weeks, were treated with plasma exchange (PEX) at presentation and throughout the remainder of pregnancy. All delivered live births in the third trimester. In women presenting between 20-29 weeks (n=6), there was one live birth following Emergency Section Caesarean Section (ESCS), presenting with intra-uterine growth retardation (IUGR) at 28 weeks. However, five pregnancies, including two sets of twins, resulted in intra-uterine fetal death (IUFD).

In women presenting with congenital TTP after 30 weeks gestation (n=11), there were 11 live births and no fetal losses. Some, but not all women received plasma therapy, relating to the diagnosis of acute TTP (Table 1).

Pregnancies following the diagnosis of congenital TTP

Ten women had fifteen live births after a diagnosis of cTTP was made. They were actively monitored and treated throughout pregnancy and the postpartum period. There were no maternal or fetal deaths and all deliveries were in the 3rd trimester. Maternal symptoms during pregnancy were reduced compared to their index cases.
and headache was the only documented symptom following treatment during pregnancy.

Two patients have been treated successfully with BPL 8Y (BioProducts Laboratory, Elstree, Hertfordshire, UK) during pregnancy, one due to severe anaphylaxis to plasma, and the other at the patients request. BPL is an intermediate purity Factor VIII concentrate, which contains a relatively high concentration of ADAMTS13\(^\text{10}\). Both pregnancies resulted in a successful outcome. In all cases, delivery was induced by 38 weeks gestation, in view of our observed increased risk of complications later in pregnancy in congenital TTP.

Five women with cTTP that presented initially in pregnancy have had subsequent episodes of TTP outside pregnancy, despite having no prior symptoms. All five of these women now receive maintenance plasma infusion (PI). One patient (case 23) presented in her early 50s with recurrent stroke and congenital TTP was confirmed during this admission but was retrospectively evident in her single pregnancy 28 years previously. Case 6 had strokes in her early sixties associated with thrombocytopenia and is on maintenance PI. She had no other documented thrombocytopenic episodes since her pregnancies.

**Maternal symptoms associated with cTTP**

A range of clinical features was observed (Figure 2). Many of these were symptoms typically associated with TTP. However, there were features that could prompt a diagnosis of other pregnancy-associated thrombotic microangiopathies (TMAs), such as pre-eclampsia, proteinuria, renal impairment. Neurological symptoms including headache, migraine, blurred vision and TIAs and proteinuria were prominent in the congenital TTP women in pregnancy. However, symptoms alone cannot differentiate congenital from acquired TTP.
Mutational analysis of ADAMTS13 in pregnancy associated onset congenital TTP

The ADAMTS 13 mutations and SNPs identified in these pregnancy associated TTP cases are outlined (Table 1). The most striking feature is the predominance of the exon 24 missense mutation c.3178C>T which was found in a homozygous (n=6) or part of a compound heterozygous (n=11) variation in seventeen women. Two of the polymorphisms identified, R7W and A1033T appeared co inherited with R1060W, present in 74% and 70% of cases respectively. All the Caucasian women who presented with TTP episodes following pregnancy had heterozygous deletions in conjunction with an other heterozygous mutation. We also identified 8 novel mutations, 4 point mutations (cases 13, 15, 16,17), and 4 deletions (cases 1,2, 5,14, 16) (Supplementary data-table 1).

B. Acquired TTP presenting in pregnancy (n=12)

Twelve women had acute pregnancy-associated TTP with an acquired phenotype, ADAMTS13 activity <10% at presentation and detectable autoantibodies (IgG) to ADAMTS 13 (median 44% range 7.5-120%).

Index cases of acquired pregnancy associated TTP

Two women presented with TTP before 20 weeks gestation. One pregnancy resulted in in utero fetal death (IUFD). In the other, treatment resulted in complete remission of TTP, but the pregnancy was terminated because of unrelated fetal chromosomal abnormalities. Four women presented with TTP between 21-29 weeks gestation. These resulted in one live birth, and 3 IUFDs. Six women presented after 30 weeks gestation all of the pregnancies resulted in live births. Presenting clinical features were similar to congenital TTP patients (Table 2). On diagnosis, women received PEX and immunosuppression with steroids as per standard TTP guidelines12.

Subsequent pregnancies in patients with a history of acquired TTP in pregnancy

There were no maternal losses in any of the acquired cases, either at presentation or in subsequent pregnancies.
Subsequent to the index pregnancy, 6 women had a further 8 pregnancies resulting in six live births in the third trimester. ADAMTS13 activity at the onset of pregnancy was 46% (range 9-80%). One pregnancy was associated with an acute relapse of TTP at 6 weeks gestation resulting in termination of pregnancy (TOP). Another resulted in IUFD in the second trimester. Amongst the successful pregnancies, one required treatment during pregnancy and had a relapse post partum. ADAMTS13 activity was normal at the beginning of pregnancy but reduced to <10% in the 2nd trimester. Oral steroids and weekly PEX were started and ADAMTS 13 activity increased to 40% in the 3rd trimester. The pregnancy continued uneventfully resulting in a live birth, but she relapsed 1 week following delivery. Two women received low dose aspirin only, one received azathioprine and LMWH throughout pregnancy. (Table 3). ADAMTS13 activity was monitored throughout pregnancy in all cases.

Use of elective rituximab in non-pregnant state

One woman was given pre-emptive Rituximab when not pregnant. She had a history of two previous mid-trimester stillbirths and an acute TTP relapse in both pregnancies. ADAMTS13 activity levels were <5% both during pregnancy and in the non-pregnant state, and she had high anti-ADAMTS 13 IgG levels (120%). She only developed acute TTP during pregnancy. She received rituximab 375mg/m² x 6 doses electively, with reduction of the anti-ADAMTS13 IgG antibody to below the normal range, and increased ADAMTS13 activity. She subsequently had two full term normal deliveries, getting pregnant 12 months after Rituximab therapy. During her first pregnancy she had PEX every 2 weeks. In her 2nd pregnancy, one year later, she had no plasma therapy, but monitoring of ADAMTS13 activity only. In both pregnancies, she received low dose aspirin and prophylactic LMWH.

C. Pregnancy in women with a previous history of TTP (not associated with pregnancy) n=12

Twelve women with a history of acute, acquired, TTP, not related to pregnancy, have had 18 pregnancies including 2 sets of twins (Table 4). In all cases, regular monitoring of ADAMTS 13 levels was undertaken, at least each trimester, if the
ADAMTS 13 is normal. Any reduction in ADAMTS13 levels requires more frequent monitoring. All women received LDA +/- LMWH prophylaxis. ADAMTS13 activity at the onset of pregnancy was 67% (range 43-89%). Women with normal ADAMTS13 activity at the beginning of pregnancy did not appear to have TTP-associated complications or relapse during pregnancy. However, in one case, there was a reduction in ADAMTS 13 levels below 10%, intervention with elective PEX therapy was undertaken for a short period, but there was no clinical relapse. A further case had normal ADAMTS13 throughout her 2nd pregnancy but developed acute lupus requiring immunosuppressives. She had no previous history of lupus. There were no TTP relapses in pregnancy. All delivered at term, and there was only one fetal loss which was unrelated to TTP (due to b-haemolytic streptococcus infection). The patient had received Rituximab 3 months before her twin pregnancy, but it was not felt to have contributed to the fetal loss. Three other patients had received rituximab 6 to 48 months before conceiving with no complications for mother or fetus. One patient had TTP associated with Human Immunodeficiency Virus (HIV). She continued highly active anti-retroviral therapy (HAART) throughout pregnancy with normal ADAMTS13 activity with no complications.

Histopathology

Placental histology was available for review in 15 deliveries from 13 mothers. Of these, 3 were first trimester miscarriages. Of 5 untreated congenital cases (gestation 23-33 weeks), all had distal villous hypoplasia and 3 of them had acute atherosis. A common feature was widespread placental ischaemia with infarcts of varying ages. Of 4 treated congenital cases (34-37 weeks), all were normal, including a post-treatment delivery at 34 weeks in the same mother who had a 27 week delivery with distal villous hypoplasia before treatment. Only 2 acquired cases had histology, an untreated IUFD at 23 weeks with hydrops and fetal anaemia, but no other placental lesion, and one post-treatment normal placenta delivered at 34 weeks (Figure 3).

Results summary (Figure 4)
Overall, 23 of 35 (66%) of the women presenting with TTP for the first time in pregnancy had late onset congenital TTP (one patient had already been diagnosed following a positive family history). In congenital TTP cases, preceding the diagnosis, fetal survival was 22/38 (58%) compared with 100% for actively managed cases following the diagnosis. Maternal survival was 100% in both circumstances within this cohort. 5/23 of the congenital cases (20%) required regular plasma infusions following presentation with TTP in pregnancy, despite having had no previous history before pregnancy.

In acquired TTP, the overall fetal survival was 58% (7 of 12). Excluding those cases presenting in the post partum period, fetal survival was 65% (5 of 9) in the index pregnancy and 75% (6 of 8) in subsequent pregnancies.

Considering all pregnancies together, both congenital and acquired cases, 46% of the 52 pregnancies associated with TTP presented after 30 weeks or postpartum, 38% between 20-29 weeks and 15% less than 20 weeks gestation. The presentation of TTP was more commonly in the postpartum period in acquired compared with congenital cases, which presented more frequently in the 3rd trimester.

Discussion

Pregnancy may be a precipitating factor in acute TTP and there is a risk of relapse during subsequent pregnancies. To date, the phenotype of TTP during pregnancy has not been well documented, particularly relating to its heterogeneous clinical presentation and management in future pregnancies. TTP should be excluded in pregnancy associated thrombotic microangiopathies. We present the largest cohort of women with a history of TTP presenting in pregnancy and describe the outcomes of index pregnancies, as well as previous pregnancies and subsequent actively managed pregnancies.

In our cohort, 66% of women presenting with acute TTP in pregnancy or the immediate post partum period had late onset, previously undiagnosed, congenital disease. In these cases, pregnancy was the initial and often the only precipitant of
TTP. Throughout subsequent pregnancies, these women received elective ADAMTS13 replacement in conjunction with antithrombotic agents, resulting in uniformly successful outcomes with no further fetal losses. Indicators of the successful management include improved fetal growth and placental histology.

In contrast to previous evidence suggesting that the most common presentation of TTP was in the second trimester\(^{12}\), our data documents the majority of presentations after 30 weeks gestation. However, the authors of the previous study were using pooled published data from over 50 years and acknowledged that few cases had ADAMTS13 assays to confirm the diagnosis. This further highlights the difficulty in distinguishing clinically between the obstetric TMAs, such as pre eclampsia or HELLP.

Differentiation of congenital or acquired TTP using ADAMTS13 assays, is required to guide the need for immunosuppressive therapy essential for acquired TTP but unnecessary in congenital disease. Furthermore, confirmation of a congenital phenotype is needed to ensure regular plasma therapy throughout subsequent pregnancies because of the high risk of fetal loss and relapsing TTP if untreated. The outcome of pregnancy in women presenting with either congenital or acquired TTP is closely related to the gestation at presentation. Pregnancy loss typically occurred in the 2\(^{nd}\) trimester for both groups. Prompt diagnosis and treatment before 20 weeks was surprisingly associated with positive pregnancy outcomes. This suggests that early and later pregnancy presentations result in a situation where there is adequate placental function to avoid the development of severe IUGR which is the most common cause of fetal loss. TTP is likely to be the only TMA presenting in the 1\(^{st}\) trimester of pregnancy. However, maternal and fetal complications (such as hypertension and premature birth, respectively) remain a risk, and mandate careful specialist multi-disciplinary team monitoring and induction of delivery before full term.

From our data, TTP (especially previously undiagnosed congenital disease) should be considered in the differential diagnosis of, in particular, mid-trimester pregnancy losses and atypical presentation of pregnancy-associated TMAs, and ADAMTS13 activity assay undertaken.
Previous published literature on congenital TTP and pregnancy is sparse\textsuperscript{13,14}. Recent data suggest the incidence of congenital TTP is 1 in 200,000 pregnancies\textsuperscript{15}. The French group describes a poor outcome in presentations in the 2\textsuperscript{nd} trimester and in subsequent pregnancies there was 100\% relapse in cTTP women who received no plasma therapy. In a Japanese series of nine women with congenital TTP, fetal loss was 50\%, and all but one of the surviving babies was premature. The exception received plasma infusions from 8 weeks’ gestation until term\textsuperscript{16}. Confirmation of the high rate of maternal and fetal complications has been presented. The symptoms may be difficult to differentiate from pre eclampsia\textsuperscript{17}. The recommendation from our cohort for subsequent pregnancies in women with congenital TTP is regular plasma infusion (10mls/Kg) from 8-10 weeks gestation every 2 weeks in combination with low dose aspirin (LDA). Plasma infusion usually increased to weekly from 20 weeks gestation and delivery aimed at 36-38 weeks gestation. If platelet counts drop below 150 x 10\textsuperscript{9}/L, an increase in therapy at any stage is required.

In our cohort, 17 of the 23 women with congenital TTP had a missense mutation, c3178C>T, in exon 24 (p.R1060W), which has previously been reported in adult-onset congenital TTP\textsuperscript{4,5}, but there is a higher proportion of cases with this abnormality than expected in this cohort. Similar findings were confirmed in the French cohort, with 8/10 cTTP cases having this heterozygous mutation\textsuperscript{15}. Functionally, the mutation causes severe intracellular retention of ADAMTS13 (<5\% secretion), without affecting activity\textsuperscript{4}. The presence of R7W and A1033T polymorphisms were higher than reported in European normal controls (13\% and 2\% respectively). Their action as positive modifiers of ADAMTS 13 expression\textsuperscript{18} with this mutation may explain the quiescent clinical course until the stress of pregnancy.

However, the genetic defects alone do not completely explain the clinical presentation. None of these 23 cases had previous TTP episodes before pregnancy, but 20\% required regular treatment following pregnancy for TTP. Four of the 5 women were Caucasian and had associated deletions rather than point mutations. Furthermore, even within the same molecular defect, clinical presentation differed (for example cases 1 and 2). There were cases of fetal survival before congenital TTP was diagnosed and no treatment received. However, there were maternal symptoms described throughout pregnancy, which were associated with morbidity.
There were eight further novel genetic defects identified that have not been previously described. Two of these mutations (in cases 13 and 16), may affect glycosylation sites, important in modulating ADAMTS 13 activity and secretion\textsuperscript{19}.

Successful pregnancy outcome can be achieved after acquired TTP is diagnosed in pregnancy\textsuperscript{20-22}. The risk of recurrence in subsequent pregnancies is reported to be approximately 50\%\textsuperscript{12,24}. In our cohort, with only one post partum relapse and no maternal deaths, which remains a risk\textsuperscript{25}. Regular monitoring of routine laboratory parameters and ADAMTS 13 levels, which was not documented in other case series allows for elective treatment\textsuperscript{26}.

In women with a history of acquired non-pregnancy related TTP, ADAMTS13 activity at the onset of subsequent pregnancy appears to be a good indicator of the risk of relapse\textsuperscript{21}. Our data suggest that women with previous acquired non-pregnancy related TTP and normal ADAMTS13 activity at the onset of pregnancy, which maintain normal ADAMTS13 activity, do not usually relapse. Monitoring of ADAMTS13 activity in subsequent pregnancies in women with a history of acquired TTP is advisable with plasma therapy started electively if ADAMTS13 activity falls <10\%, to prevent microvascular thrombosis which could affect placental function\textsuperscript{27}. There are no guidelines on frequency of ADAMTS13 activity assays, but for acquired TTP cases we recommend monitoring at the start of pregnancy and at least in each trimester.

Where low ADAMTS13 preceded pregnancy, rituximab was used electively with successful pregnancy outcomes. Patients were advised to wait 12 months following rituximab before conceiving. However, some women became pregnant before this with no ill effects to mother or fetus. Indeed, waiting until normalisation of CD19 lymphocyte levels, at approximately 6 months with no detectable serum rituximab, may be satisfactory\textsuperscript{28}.

A limiting factor of this work is the reporting of TTP cases to the registry, which is voluntary. The heterogeneous nature of presentations cannot be controlled for, but there was a standard therapeutic management of subsequent cases, particularly in congenital TTP.
In conclusion, pregnancy-associated TTP was due to late onset congenital TTP in the majority of our cohort. These women require plasma therapy; PEX at acute presentation and infusion as prophylaxis throughout subsequent pregnancies. Early (<20 weeks) and late pregnancy (>30 weeks) presentations were associated with a good outcome while presentations between 20-29 weeks gestation were more often associated with severe fetal IUGR and fetal death. A high proportion of the patients had the R1060W mutation and 20% of the congenital cohort went on to require regular ADAMTS 13 replacement following pregnancy. ADAMTS13 activity and inhibitor/antibody status is necessary for TTP subtype identification, management of subsequent pregnancies and differentiation from other pregnancy-associated TMAs. Importantly our data suggest that women with previous acute TTP may plan future pregnancies with appropriate specialist management.
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Authorship Contributions:

Designed research: MS, KL

Provided patient samples/data: MS, AC, DC, RR, HW, VM, RA, GE, SM, FNA, SM, RM, WL, MN, POB

Performed laboratory analysis, MS, KL, RSC, VM, RS, MU

Wrote the paper: MS, KL, HW, MT, RS, POB

Reviewed the manuscript: MS, MU, KL, AC, DC, RR, HW, MT, RS, POB, GE, FNA, RS, POB

Conflict of Interest Disclosure:

The authors have confirmed there are no relevant financial conflicts of interest.

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Reference List


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<td>PI/PEX</td>
<td>IUFD</td>
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<td>3. 20/40</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. 6/40</td>
<td>Miscarriage</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5. 38/40*</td>
<td>daily PEX &amp; Steroids</td>
<td>Live birth 37/40</td>
</tr>
<tr>
<td></td>
<td>6. 37/40</td>
<td>LDA &amp; LMWH throughout. PI from 10/40 every 2 weeks until 20 weeks, then continued weekly. 1 PEX pre &amp; post delivery</td>
<td>Live birth</td>
</tr>
<tr>
<td>13</td>
<td>1. 38/40*</td>
<td>PEX, LDA</td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>2. 37/40</td>
<td>PEX every 2 weeks from 12 weeks, continued with PI every 2 weeks from 2nd trimester</td>
<td>Live birth</td>
</tr>
<tr>
<td>14</td>
<td>1. 39/40*</td>
<td>PEX</td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>2.38/40</td>
<td>weekly PI in 3rd trimester, LMWH &amp; LDA</td>
<td>Live birth</td>
</tr>
<tr>
<td>15</td>
<td>1. 27/40</td>
<td>Platelet transfusion</td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>2. 34/40*</td>
<td>PEX, steroids, LDA, LMWH, IVIG,</td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>3. 36/40</td>
<td>BPL 8Y x 2/week throughout pregnancy and 4 weeks PP. 2 X PEX pre delivery</td>
<td>Live birth</td>
</tr>
<tr>
<td>16</td>
<td>32/40*</td>
<td>Daily PEX to TTP remission then weekly until delivery</td>
<td>Live birth 37/40</td>
</tr>
<tr>
<td></td>
<td>1. 20/40 (twins)</td>
<td>IVlg, Prednisolone, Platelets, PEX</td>
<td>IUFD 25/40</td>
</tr>
<tr>
<td></td>
<td>2. 39/40</td>
<td>PI throughout pregnancies. Platelets at delivery</td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>3. 37/40</td>
<td></td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>4. 37/40*</td>
<td></td>
<td>Live birth</td>
</tr>
<tr>
<td></td>
<td>Case Number</td>
<td>Outcome</td>
<td>Treatment Notes</td>
</tr>
<tr>
<td>---</td>
<td>-------------</td>
<td>---------</td>
<td>-----------------</td>
</tr>
<tr>
<td>17</td>
<td>14/40*</td>
<td></td>
<td>Daily PEX until remission then weekly PEX to delivery Live birth 35/40</td>
</tr>
<tr>
<td>18</td>
<td>(known from positive FH)</td>
<td>37/40</td>
<td>LDA, PI every 2 weeks, then weekly from 25/40</td>
</tr>
<tr>
<td>19</td>
<td>1.20/40</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 24/40 (twins)*</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. 6/40</td>
<td>miscarriage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. 37/40</td>
<td>Plasma Treatment x 2/week from 12 weeks Live birth</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>33/40</td>
<td>Steroids</td>
<td>Live birth</td>
</tr>
<tr>
<td>21</td>
<td>1. 34/40 (twins)</td>
<td>Live birth</td>
<td>Platelets,</td>
</tr>
<tr>
<td></td>
<td>2. 28/40*</td>
<td>PEX</td>
<td>Live 29/40</td>
</tr>
<tr>
<td>22</td>
<td>1. 24/40</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. 26/40</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. 27/40</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/5/6: 6-12/40</td>
<td>3X miscarriages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. 27/40</td>
<td>Live birth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. 20/40*</td>
<td>LDA, LMWH, PI, PEX IUFD 28/40</td>
<td></td>
</tr>
<tr>
<td>23§</td>
<td>36/40</td>
<td>Live birth</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1: Late onset Congenital TTP presenting in pregnancy**

**Key:** PI (plasma infusion), PEX (plasma exchange), IUFD (in utero fetal death), LDA (low dose aspirin), LMWH (low molecular weight heparin), LFTs (liver function tests), TIAs (transient ischaemic attacks), C/P(chest pain), trop T (troponin T), HBP (high blood pressure), PET (pre eclampsia), Plts (platelet transfusion), IVIg (intravenous immunoglobulin), PEs (pulmonary emboli).

* denotes the pregnancy TTP was diagnosed.

§ denotes retrospective diagnosis
Figure Legend

Figure 1: Summary of the management of a patient presenting with acute TTP

Figure 2: Symptoms documented in women presenting with pregnancy associated TTP

Figure 3: Placental histology in women with pregnancy associated TTP and following treatment
3a Pre-treatment delivery at 28 weeks’ gestation: placenta showing an infarct (arrow).
3b Pre-treatment delivery at 28 weeks’ gestation: distal villous hypoplasia, indicating ischaemia. (H&E x200)
3c Subsequent delivery following treatment at 36 weeks’ gestation: normal villi. (H&E x200)

Figure 4: Summary of patients presenting with TTP in Pregnancy. A summary of all the cases of women presenting with congenital and acquired TTP in pregnancy and the resulting fetal outcomes.
Figure 1: Summary of the management of a patient presenting with acute TTP in pregnancy

1. Thrombocytopenia & MAHA in pregnancy
   (associated findings may be PET, HBP, renal symptoms)

2. Blood film, coagulation, LDH, reticulocytes, LFTs

3. TMA diagnosed:
   Refer to a specialist apheresis centre
   Samples for ADAMTS 13 assays

4. PEX until TTP remission achieved

5. ADAMTS 13 <10% No evidence of antibody
   CONGENITAL TTP
   - Confirm ADAMTS 13 results and proceed to mutational analysis in remission
   - On remission/in subsequent pregnancies:
     - PI required 2 weekly from onset of pregnancy until approximately 20 weeks
       -continue weekly PI until 6 weeks post partum
   - Monitor postpartum for relapsing TTP

6. ADAMTS 13 <10% antibody present
   ACQUIRED TTP
   - Further immunosuppression may be required to attain/sustain remission, eg steroids
   - On remission/in subsequent pregnancies:
     - if persistent low ADAMTS 13 and positive ADAMTS 13 antibody, consider elective treatment eg rituximab, before subsequent pregnancy
     - Check ADAMTS13 activity at onset of pregnancy
     - Monitor at least each trimester throughout pregnancy
     - Regular routine blood counts at least monthly
     - ADAMTS 13 <10% consider elective treatment eg PEX, steroids, azathioprine
All women require specialist obstetric review, regular fetal growth scan and uterine artery Doppler monitoring. On achieving a platelet count of 50x10^9/L, start LDA. Following an acute presentation, LMWH thromboprophylaxis should be given. **Key:** MAHA (microangiopathic haemolytic anaemia), LFTs (liver function tests), PI (plasma infusion), PEX (plasma exchange)
Figure 2: comparison of maternal symptoms/presentation in congenital compared to acquired TTP

Key: HBP (hypertension), PET (Preeclampsia), TIAs (transient ischaemic attacks), Cardiac (chest pain, increased troponin T), LFTs (liver function tests), PE (pulmonary emboli), Acute collapse (requiring intubation and ventilation)
Figure 3: Placental histology in women with pregnancy associated TTP and following treatment
Figure 4: Summary of patients presenting with TTP in Pregnancy

Acute TTP in Pregnancy
N=35

Congenital TTP
23 women
53 pregnancies

Previous Obstetric History
18 pregnancies
7 Live births
11 Fetal losses
Live birth rate=39%

Index pregnancy
20 pregnancies
15 Live births
5 Fetal losses
Live birth rate=75%

Pregnancies following diagnosis of cTTP
15 pregnancies
15 Live births
Live birth rate=100%
Maternal survival=100%

Acquired TTP
12 women
20 pregnancies

Pregnancies following diagnosis of acquired TTP
8 pregnancies
6 Live births
1 Fetal loss
1 Termination*
Live birth rate=75%
Maternal survival=100%

Acute TTP presentation
12 pregnancies
7 Live births
5 Fetal losses
Live birth rate=58%

Pregnancies following diagnosis of acquired TTP
8 pregnancies

* termination <12 weeks because of severe refractory TTP
Congenital and acquired thrombotic thrombocytopenic purpura and pregnancy: presentation, management and outcome of subsequent pregnancies

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