Article Type: Main Research Article

# Severe Primary Autoimmune Thrombocytopenia (ITP) in Pregnancy: a National Cohort Study

Care, A[1], Pavord, S[2], Knight, M[3], Alfirevic Z[1].

[1]Centre for Women and Children's Health Research, University of Liverpool, Liverpool Women's Hospital, Crown Street, L8 7SS

[2]Oxford University Hospitals, Old Road, Headington, Oxford, OX3 7LE

[3]National Perinatal Epidemiology Unit (NPEU), Nuffield Department of Population Health, University of Oxford, Old Road Campus, Headington, Oxford, OX3 7LF

Corresponding Author: Dr Angharad Care

Address: University Department, Liverpool Women's Hospital, Crown Street, Liverpool, L8 7SS

Telephone Number: 0151 795 9566

Email: angharad.care@liv.ac.uk

Shortened Title: Severe ITP in Pregnancy: a National Cohort Study

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.14697

**Abstract**

**Objective** To quantify UK incidence of severe ITP in pregnancy, determine current treatment strategies and establish maternal and neonatal morbidity and mortality associated with severe ITP in pregnancy.

**Design** A prospective national cohort study

**Setting** United Kingdom

**Population** Women with severe ITP; defined as platelets <50 x $10^9$/l in pregnancy *or* antenatal treatment of isolated low platelets.

**Methods** Data collected via United Kingdom Obstetric Surveillance System (UKOSS) between 1st June 2013–31st January 2015 from all UK Consultant led obstetric units.

**Main Outcome Measure** Incidence of Severe ITP in pregnancy.

**Results** The estimated incidence of severe ITP in pregnancy is 0.83 per 10,000 maternities (95% CI 0.68-1.00). 22 pregnant women (21%) did not receive any antenatal therapy, 85 (79%) had therapy. There was no difference between asymptomatic treated and untreated cohorts in severity of disease or outcome. Postpartum haemorrhage (51%) and severe postpartum haemorrhage (21%) was reported more frequently than the reported rate in the general pregnant population (5-10%). No neonates required treatment for thrombocytopenia and there were no cases of neonatal intracranial bleeding.

**Conclusions** Current UK management of severe ITP in pregnancy results in an exceptionally low morbidity and mortality for the neonate. Mothers with ITP remain at increased risk of severe post-partum haemorrhage and should be delivered at units that have the capacity to manage

severe PPH effectively. Whilst balancing risks for pregnancy of prophylactic antenatal treatment in asymptomatic women against observed low disease morbidity, we may be over treating asymptomatic patients.

**Keywords** Platelets, Autoimmune Thrombocytopenia, Pregnancy

**Tweetable Abstract:** UKOSS study of Severe ITP in pregnancy shows exceptionally low neonatal morbidity with current UK management.

## Introduction

Primary autoimmune Thrombocytopenia (ITP) is a haemorrhagic disorder characterised by transient or persistent decrease in platelet count and, depending on the degree of thrombocytopenia, an increased risk of bleeding.[1] It is an acquired autoimmune disease involving antibody- and cell-mediated destruction of platelets.[2] ITP can present at any age, however like many other autoimmune conditions, it is commonly detected in women during reproductive years (20-40 years). The reported incidence of ITP during pregnancy ranges from 1 in 1,000 to 1 in 10,000 pregnancies.[3,4] Quantifying an incidence of severe ITP has been difficult due to the rarity of the disease, differentiating between other causes of thrombocytopenia in pregnancy and accepting changes over time in disease criteria for diagnosis. Gestational thrombocytopenia, a pregnancy specific thrombocytopenia, can be difficult to distinguish from ITP. Both diagnoses require exclusion of alternative causes, however GT is generally considered benign and platelets extremely rarely fall below $70 \times 10^9$/L, with very few cases ever described with platelets 40-50x$10^9$/L, [5] whereas ITP can be associated with maternal or neonatal bleeding risk.

Transplacental transfer of IgG platelet specific autoantibodies can induce neonatal thrombocytopenia and risk of intracranial haemorrhage (ICH) at delivery. Historically fears of bleeding risk have dominated management of ITP. In 1976, caesarean section was recommended for all ITP patients based on a reported perinatal mortality of 12% to 21%, largely resulting from birth trauma and ICH. [3] More recent studies have reported mortality rates of ITP mothers < 1% and ICH of neonates <1.5%, with only approximately 10% of neonates having platelet counts lower than $50 \times 10^9$/L. [6]

Although there is no direct correlation between neonatal and maternal platelet counts, we hypothesised that the risks of maternal and neonatal morbidity and mortality would be higher in women with more severe ITP, as shown by previous studies. [7] The aim of this study was to estimate the UK incidence of severe ITP in pregnancy, current management, and the maternal and fetal outcomes of these pregnancies using current treatment strategies. We planned to compare the two most common treatments, steroids and IVIG, to assess any difference in outcomes depending on treatment received.

## Methods

We conducted a national cohort study using the UK Obstetric Surveillance System (UKOSS) to identify pregnant women with severe ITP. Data were collected on women who delivered over a 20 month period, from 1st June 2013-31st January 2015.

### *Data source and definitions*

We adopted a pragmatic definition of severe ITP in pregnancy as follows:

*Either*

a) any woman who had been diagnosed with thrombocytopenia with a platelet count of <50 x $10^9$/l at any point in her pregnancy prior to delivery where obstetric and hereditary causes for thrombocytopenia had been excluded (i.e. Pre-eclampsia, HELLP syndrome, acute fatty liver of pregnancy, known antiphospholipid antibody syndrome or other hereditary thrombocytopenias)

*or*

b) any pregnant woman diagnosed with an isolated thrombocytopenia where a clinical decision to treat the thrombocytopenia prior to delivery of the infant had been made.

Women with immune thrombocytopenia secondary to systemic lupus erythematosus (SLE) Hepatitis C, CMV, HIV and HAART therapy or any condition where treatment of thrombocytopenia is focused on treatment of the causative disease were excluded from the study. The authors felt that the above criteria would almost certainly exclude cases of gestational thrombocytopenia (GT) based on the rarity of cases of GT with platelets <50 x $10^9$/l, with only one case report from 6715 consecutive deliveries of gestational thrombocytopenia with platelets between 40-50x$10^9$/l.[8]

By including only this cohort, we have targeted women considered "severe", both clinically and by platelet count and excluded women most likely to have GT.

The UKOSS methodology has been described in detail elsewhere.[9] In brief, UKOSS case notification cards were sent to all 202 UK hospitals with consultant-led maternity units, with a tick box list to indicate whether they had seen any cases of severe ITP in pregnancy. These units cover all deliveries in the UK, since any women with medical complications would be referred to one of these units. Prospective collection of data occurred through monthly reporting of cases by

official UKOSS reporters at each site. When a clinician returned a card indicating a case, a condition-specific data collection form was sent for completion. If a completed data collection form was not returned, up to three reminders were sent. To encourage reporting during the study period, this study was presented twice at the annual UK Obstetric Haematology Group meeting and a notification was published in the British Journal of Haematology. At the end of the study period, some haematologists in centres known to manage specialist ITP populations were approached and asked to check all local cases were notified.

Where data were missing or the response unclear, the reporting clinician was contacted. Data were collected on maternal demographics(including previous diagnosis of ITP, previous treatment for ITP received including splenectomy), maternal complications due to ITP both antenatally and postnatally, additional investigations as part of workup for ITP, antenatal management, management of labour and maternal, delivery and neonatal outcomes.

The incidence of ITP was calculated using an appropriate denominator of all deliveries in the UK for the period of the study to give rates of severe ITP per 1000 maternities.

*Statistical methods*

SPSS Statistics 22 software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for all analysis. Outcomes of pregnancy in women who had received antenatal treatment were compared with those who had received no antenatal treatment prior to labour. Non-parametric data was compared with Mann Whitney-U tests. For comparison of binary outcomes $Chi^2$ or Fishers Exact tests were used. Once data were further subdivided into groups per treatment type comparative tests were not routinely performed due to small numbers and hence low statistical power. The overall outcomes are presented as descriptive data and simple percentages.

## Results

### *Incidence of ITP*

A total of 107 pregnancies in women with severe ITP were reported to UKOSS over the 20 month period of data collection. Using statistics on maternities from the Office for National Statistics; the number of maternities for our period of study was 1,295,963. Therefore the estimate of incidence of severe ITP in pregnancy is 0.1 per 1000 maternities (0.083 per 1000 maternities, 95% CI 0.068-1.00 per 10,000) or 1 in 10,000 maternities.

### *Demographics*

Table I. shows the characteristics of women divided according to whether they received antenatal treatment for thrombocytopenia. There was no significant difference in any reported demographic characteristic. Having a known diagnosis of ITP prior to pregnancy (58%) did not appear to influence the decision to receive treatment. New presentations of ITP account for 42% of severe thrombocytopenia cases in pregnancy. The previous severity of those with known ITP, as determined crudely by the history of lowest platelet count, did not impact on the likelihood of receiving treatment in pregnancy.

### *Antenatal Therapy for Severe ITP*

Eighty-five women (79%) were given treatment prior to labour for severe primary ITP in their pregnancy. Almost all women fall into one of three treatment groups, 1) steroids, 2) IVIG or 3) steroids plus IVIG. The majority received steroids (n=38, 45% of all women treated) and three of these women received additional high dose methylprednisolone (HDMP). For one pregnancy, it was unclear if the steroids given to the woman were for obstetric or haematological indication. In

this case there was a known prior diagnosis of ITP, steroids were given on the day before and day of term vaginal delivery with a lowest platelet count in pregnancy of 148 x $10^9$/l and no symptoms of ITP reported in the antenatal period. The outcomes in this case were good for mother and neonate. Despite high platelet counts this case has been included due to steroid therapy. However, the lowest platelet count is reported here as an outlier (not shown in table V). 17 women received IVIG only (20%) and 28 were prescribed a combination of steroids and IVIG (32%). Only two women received alternative therapies; one woman had Anti-D combined with platelet transfusion and one had a combination of steroids, IVIG, azathioprine 150mg OD, platelets and fresh frozen plasma (FFP). These women will be discussed as case reports in the text and are not included in tables comparing treatment regimens.

Overall 37/107 women (35%) reported some symptoms of ITP in their pregnancy. 7 of these 37 women did not receive any treatment, they reported bruising (n=4), purpura (n=2) and gingival bleeding (n=3). Overall women who reported symptoms had a lower median platelet count in pregnancy than asymptomatic women (21 vs. 40 x $10^9$/l; p=0.0001).

All outcomes have been reported by treatment group (no treatment, steroids only, IVIG only, steroids and IVIG combined). Table S1 reports the indication or clinician's reason for providing therapy. Over half (54%) were asymptomatic of ITP but received therapy to reach a target platelet count for delivery and 37% were treated prophylactically to prevent maternal sequelae of ITP based on a low platelet count. In five women, symptoms of ITP triggered treatment, with platelets of 5, 6, 14, 17 and 30 x $10^9$/L. The symptoms reported ranged from epistaxis only to a combination of epistaxis, bruising and gingival bleeding. The woman with platelets of 14x$10^9$/l went on to receive azathioprine 150mg po od, platelets and FFP and is therefore not reported in table S1.

Treatment side effects were experienced by 7 out 83 treated women (8%) and were more commonly reported by women on a combination of IVIG and steroids, 5/28 (18%). Individual side effects are reported in Table S1. Only one woman reported more than one side effect.

*Labour Management*

Table 2 shows the onset of labour, mode of delivery, lowest platelets in pregnancy, platelets at delivery and anaesthetic choices per treatment group. The caesarean section (CS) rate in this cohort was high 42/107 (39%). The indications for CS are shown in Table S2. Instrumental deliveries were performed in 12 patients (11%). The lowest recorded cord platelet count following delivery using instrumental was $79x10^9$/L and no complications were recorded.

The reasons given for not requiring FBS are listed in Table 2. In the majority (86%) of cases there was no indication for FBS. In 5 women (7%) a concern regarding low fetal platelets was cited as a contraindication to the test, two women had an FBS performed.

The overall median platelet count at the time of delivery was 64 x $10^9$/l. Untreated women had lower platelets at delivery (56 x $10^9$/l), compared with treated women, but the difference is neither statistically nor clinically significant (p=0.331).

Fourteen women received an epidural during labour (median platelet value was 102 x $10^9$/l; range 14-152 x $10^9$/l). Twelve women had spinal anaesthesia for CS (median platelet value was 93 x $10^9$/l; range 23-154 x $10^9$/l). In total there were six women who had a regional anaesthetic with platelets below 80 x $10^9$/L: platelets of 14, 23, 36, 43, 64 and 67 x $10^9$/l respectively.

*Pregnancy Outcomes*

There were no cases of epidural, caesarean section wound or perineal haematoma following delivery. (Table 3)

The most common definition of PPH is estimated blood loss ≥500 mL after birth. Severe postpartum haemorrhage (SPPH) is defined as blood loss from the genital tract of ≥1000 mL in the first 24 hours after the delivery.[10] Using these definitions the rate of PPH in this cohort is 56/107 (52%), the rate of SPPH is 22/107 (21%). One woman with a platelet count of 55 x $10^9$/L after normal vaginal delivery who had needed multiple therapies, including azathioprine, required a hysterectomy for a subsequent SPPH. The median platelet count for all women diagnosed with PPH was 58 x $10^9$/L (range 12 – 148 x $10^9$/L) which was significantly lower than the median value for those who did not have a PPH; 132 x $10^9$/L (range 94 – 170 x $10^9$/L, p value 0.029), there was no difference between treated and untreated groups.

There was one case of psychotic post-partum depression which is a recognized complication of prolonged steroid use in pregnancy.

*Neonatal Outcomes*

From 107 pregnancies of 110 fetuses (6 twins, 104 singletons), 108 babies were liveborn. There was one case of stillbirth thought to be unrelated to thrombocytopenia. One woman had an early miscarriage at less than 12 weeks of pregnancy. However, the rate of early pregnancy loss for women with severe ITP will be extremely underestimated; most pregnancies reported here were successful ongoing pregnancies identified after the pregnancy was booked during the first trimester.

Platelet counts measured at birth were available for 56 babies. The median birth platelet count was 193 x $10^9$/l (range 59 – 373). Seven babies (12%) had platelet counts <100 x $10^9$/l at birth (Table S3).

Seventy seven babies had recorded platelet count in the neonatal period below 150 x $10^9$/l, these are shown in Table 4. The remaining 54 (70%) did not have any reported thrombocytopenia. Two cases of thrombocytopenia could be attributed to concurrent neonatal sepsis.

The additional two neonates not reported in the main tables (their mothers had alternative therapy with Anti D or azathioprine, platelets and FFP) were both liveborn without thrombocytopenia; one baby was temporarily admitted to the neonatal intensive care unit for treatment of jaundice.

No babies received treatment for thrombocytopenia and there were no cases of intracranial hemorrhage or neonatal deaths. Sixteen infants (70%) were reported to have spontaneous recovery of their platelets. For the remaining seven infants spontaneous recovery of the platelets was not documented but the neonates were all discharged from hospital without treatment for thrombocytopenia.

## Discussion

### *Main Findings*

In summary, our data suggest that the overall incidence of severe ITP in pregnancy is 0.83 in 10,000 maternities in the UK (95% CI 0.68-1.00). Severe ITP in pregnancy carries a high risk for severe postpartum haemorrhage and outcomes for neonates were better than expected with no cases of intracranial haemorrhage or death.

There is variation in treatment of severe ITP in pregnancy among clinicians in the UK at present. This allowed us to directly compare outcomes of patients who did not receive antenatal treatment with those who had therapy without any obvious difference in the characteristics or severity of ITP and interestingly we found no difference in outcomes between these groups. Most women in the treatment group (91%) are treated prophylactically due to platelet count alone and not because of symptoms of ITP (Figure S1).

***Strengths***

The strengths are in the UKOSS methodology used to obtain data on a well phenotyped cohort of women with severe ITP. All cases were reviewed by the UKOSS team to ensure they met the case definition before inclusion and all four authors reviewed the cases individually for agreement on inclusion.

This is the largest cohort study of ITP in pregnancy to date and the first study to report separately on the effects of different treatments.

***Limitations***

UKOSS data relies on reporting of monthly cases. Under reporting may occur and to account for this a 95% confidence interval has been included with our estimate of incidence. Due to worst case reporting bias cases with poor outcomes will likely get a higher local profile, and are more likely to be brought to the attention of local UKOSS reporters. We believe that our conclusions regarding safety of severe ITP in pregnancy are unlikely to be affected by potential under reporting.

The non-treated and treated cohorts may not be directly comparable as there maybe unknown selective pressure towards more severe cases receiving treatment. Additionally, we do not have serial platelet count data from pregnancy or post pregnancy, only the lowest platelet count and we are not recommending a change in practise based on this data.

This data is only for women with platelets <50 x $10^9$/L and those requiring antenatal treatment, we cannot comment on neonatal morbidity and mortality risks for patients with platelets above 50 x$10^9$/L who do not receive treatment.

***Interpretation***

Primary PPH currently affects 5 in 100 pregnancies in the UK[11] and the risk in our severe ITP cohort is approximately ten times higher. This is irrespective of treatment, but statistically more likely in women with lower platelet counts at delivery. When considering life-threatening haemorrhage (blood loss of ≥2.5 litres, >5 units of blood transfused or treatment for coagulopathy after an acute bleed), the rate in Scotland is estimated at 3.7/1000 maternities[12] compared to 3.7/100 cases in this cohort (n=4). There are several possible reasons for this frequency. Firstly, delivering by caesarean section (CS) loses more blood on average than delivering vaginally. Using an estimated blood loss ≥1000 after CS[13] as the definition of PPH, the rate would decrease to 24%, which is still five times higher than estimates from the literature. Secondly there is criticism of the reported incidence of PPH in the general population; clinicians typically underestimate the amount of blood lost at delivery[14] and therefore the discrepancy may not be as high as reported figures suggest. Thirdly in women with low platelets clinicians may subconsciously over-estimate blood loss to ensure closer monitoring in the immediate post-partum period, leading to over-reporting. Lastly the increase may be a real phenomenon

suggesting an abnormality in platelet count or function that predispose ITP mothers to a primary PPH.

Prevention of PPH from uterine atony requires blood vessel vasoconstriction. Platelets have been shown to contribute towards vasoconstriction through the release of thromboxane A2. Platelet function in severe ITP may be affected by immune complexes formed by platelet antibody. Women with Von Willebrand Disease (VWD) have reported PPH rates as high as 29%.[15] Therefore our data suggest that there may be a role of platelet function in prevention of PPH or alternatively it may be a combination of over reporting, high CS rate and chance finding in a small cohort. This finding should be validated in further work.

For placement of safe regional anesthesia the minimum platelet count is unknown and most anaesthetists will place a regional anesthetic if the platelet count is $\geq 80 \times 10^9$/l.[3] Only six cases had epidurals inserted with platelets $<80 \times 10^9$/l and no further recommendations regarding a minimal platelet count can be made given this small number.

In order to put our results in the context of the currently available evidence we have reviewed all papers describing case-series or cohorts that included at least ten women with ITP in pregnancy. Figure S1 shows the diagram of information acquisition. 28 papers reporting outcomes of ITP in pregnancy have been summarised in Table S4 and our UKOSS data has been included for comparison.

58% of women had known ITP prior to pregnancy, which is in keeping with estimates from 19 other studies (median 58%, range 33-87%) and demonstrates that almost half of ITP in women of reproductive age will be detected for the first time in pregnancy.

Our cohort has a high Caesarean section (CS) rate which matches the median CS rate from the literature. The most common reason for unplanned or emergency CS was fetal compromise. This may be linked to an earlier recourse to CS if there are concerns for fetal wellbeing, as fetal blood sampling is not used due to concerns regarding thrombocytopenia in the baby. Additionally, a higher rate of induction of labour (38%) exists in this cohort compared to the English national rate of 13.2%[16] increasing the likelihood of failed induction of labour resulting in CS.

Despite better than expected outcomes for this cohort in its entirety, it is possible some women are receiving unnecessary treatments which have the potential to cause harm in pregnancy. For example, one woman receiving prophylactic steroids had postpartum psychosis, a recognized complication of steroids and an obstetric and psychiatric emergency due to the risk of suicide or infanticide. The baseline level of post-partum psychosis in the pregnant population is very low at 1 in 1000 women and incidence of steroid psychosis is not known for the pregnancy population. There is insufficient data to attribute this episode of postpartum psychosis directly to corticosteroid use as we have not collected data regarding background psychiatric risk. However, in women who are well and do not report symptoms of bleeding with severe thrombocytopenia in pregnancy caused by ITP, the authors suggest it may be reasonable not to give steroids or IVIG treatment in the antenatal period and cover delivery with blood products alone if surgical intervention was required. A randomised clinical trial would normally be recommended to provide definitive evidence that this is a safe alternative to prophylactic therapy. However a definitive randomized trial aiming to quantify the difference in benefits and harm of various treatment options is unlikely to be feasible. Even a multicentre study with more 1,000 randomised women would not be large enough to exclude a possibility of clinically important difference in the risk of serious neonatal complications between treatment groups. A national

data registry of severe ITP with internationally agreed individual patient data collections items (demographics, covariates, outcomes) seems a logical alternative.

## Conclusion

The estimated incidence of severe ITP in pregnancy is 1 per 10,000 maternities. Current UK management of severe ITP in pregnancy results in an exceptionally low morbidity and mortality for the neonate. Mothers with ITP remain at increased risk of severe post-partum haemorrhage and should be delivered at units that have the capacity to manage severe PPH effectively. Whilst balancing the risks for pregnancy of prophylactic antenatal treatment in asymptomatic women against an observed low disease morbidity, we may be over treating asymptomatic patients and exposing them to unnecessary side effects of prophylactic platelet treatment.

## Acknowledgments

The authors would like to thank the UK Obstetric Surveillance System (UKOSS) reporting clinicians who notified cases and completed the data collection forms.

## Disclosure of Interests

All authors, AC, SP, MK and ZA, have no competing interests. MK is funded by an NIHR Research Professorship. The views expressed in this publication are those of the author(s), and not necessarily those of the NHS, the NHIR, or the Department of Health. The ICMJE disclosure forms are available as online supporting information.

## Contribution to Authorship

AC, SP, MK and ZA reviewed all the cases submitted to UKOSS for inclusion to ensure they met inclusion criteria. AC drafted this article, which was subsequently critically reviewed and revised by SP, MK and ZA.

## Details of Ethical Approval

The NRES Committee North West Lancaster reviewed the above application on 14th February 2013 and granted ethical approval (REC reference: 13/NW/0133).


## Funding

This work was supported by a grant from The ITP Support Association, UK (grant to AC and ZA).


## References


1. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. *Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group.* Blood. 2009;113(11):2386-93.
2. Cuker A, Cines DB. *Immune thrombocytopenia.* Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2010;2010:377-84.
3. Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussel JB, et al. *International consensus report on the investigation and management of primary immune thrombocytopenia.* Blood. 2010;115(2):168-86.
4. Segal JB, Powe NR. *Prevalence of immune thrombocytopenia: analyses of administrative data.* Journal of thrombosis and haemostasis : JTH. 2006;4(11):2377-83.
5. Gernsheimer T, James AH, Stasi R. *How I treat thrombocytopenia in pregnancy.* Blood. 2013;121(1):38-47.
6. Burrows RF, Kelton JG. *Fetal thrombocytopenia and its relation to maternal thrombocytopenia.* The New England journal of medicine. 1993;329(20):1463-6.
7. Jensen JD, Wiedmeier SE, Henry E, Silver RM, Christensen RD. *Linking maternal platelet counts with neonatal platelet counts and outcomes using the data repositories of a multihospital health care system.* American journal of perinatology. 2011;28(8):597-604.
8. Burrows RF, Kelton JG. *Thrombocytopenia at delivery: a prospective survey of 6715 deliveries.* American journal of obstetrics and gynecology. 1990;162(3):731-4.

9. Knight M, Kurinczuk JJ, Tuffnell D, Brocklehurst P. *The UK Obstetric Surveillance System for rare disorders of pregnancy.* BJOG : an international journal of obstetrics and gynaecology. 2005;112(3):263-5.
10. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. *Epidemiology of postpartum haemorrhage: a systematic review.* Best practice & research Clinical obstetrics & gynaecology. 2008;22(6):999-1012.
11. Fullerton G, Danielian PJ, Bhattacharya S. *Outcomes of pregnancy following postpartum haemorrhage.* BJOG : an international journal of obstetrics and gynaecology. 2013;120(5):621-7.
12. Brace V, Kernaghan D, Penney G. *Learning from adverse clinical outcomes: major obstetric haemorrhage in Scotland, 2003-05.* BJOG : an international journal of obstetrics and gynaecology. 2007;114(11):1388-96.
13. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. *Treatment for primary postpartum haemorrhage.* The Cochrane database of systematic reviews. 2014;2:Cd003249.
14. Schorn, MN. Measurement of Blood Loss; review of the literature. J Midwifery Womens Health. 2010 Jan-Feb;55(1):20-7.
15. Lak M, Peyvandi F, Mannucci PM. *Clinical manifestations and complications of childbirth and replacement therapy in 385 Iranian patients with type 3 von Willebrand disease.* British journal of haematology. 2000;111(4):1236-9.
16. NHS Maternity Statistics - England 2013-14. Publication date: Jan 28 2015. Date of access: Jun 17 2016. (Available at http://www.hscic.gov.uk)
17. Al-Jama, F.E. Rahman J, Al-Suleiman SA, Rahman MS. *Outcome of pregnancy in women with idiopathic thrombocytopenic purpura.* Aust N Z J Obstet Gynaecol, 1998. 38(4): p. 410-3.
18. Ali R, Ozkalemkaş F, Ozçelik T, Ozkocaman V, Ozan U, Kimya Y, et al. *Idiopathic thrombocytopenic purpura in pregnancy: a single institutional experience with maternal and neonatal outcomes.* Ann Hematol, 2003. 82(6): p. 348-52.19. Barbui T, Cortelazzo S, Viero P, Buelli M, Casarotto C. *Idiopathic thrombocytopenic purpura and pregnancy. Maternal platelet count and antiplatelet antibodies do not predict the risk of neonatal thrombocytopenia.* Ric Clin Lab, 1985. 15(2): p. 139-44.
20. Cook RL, Miller RC, Katz VL, Cefalo RC. *Immune thrombocytopenic purpura in pregnancy: a reappraisal of management.* Obstet Gynecol, 1991. 78(4): p. 578-83.
21. De Carolis, S, Noia G, De Santis M, Trivellini,C. Mastromarino, C. De Carolis, MP. et al. *Immune thrombocytopenic purpura and percutaneous umbilical blood sampling: an open question.* Fetal Diagn Ther, 1993. 8(3): p. 154-60.
22. Devendra, K. and Koh LP. *Pregnancy in women with idiopathic thrombocytopaenic purpura.* Ann Acad Med Singapore, 2002. 31(3): p. 276-80.
23. Fujimura K, Harada Y, Fujimoto T, Kuramoto A, Ikeda Y, Akatsuka, J. et al. *Nationwide study of idiopathic thrombocytopenic purpura in pregnant women and the clinical influence on neonates.* Int J Hematol, 2002. 75(4): p. 426-33.
24. Fujita A, Sakai R, Matsuura S, Yamamoto W, Ohshima R, Kuwabara H, et al. *A retrospective analysis of obstetric patients with idiopathic thrombocytopenic purpura: a single center study.* Int J Hematol, 2010. 92(3): p. 463-7.
25. Gasim, T. *Immune thrombocytopenic purpura in pregnancy: a reappraisal of obstetric management and outcome.* J Reprod Med, 2011. 56(3-4): p. 163-8.

26. Kasai J, Aoki S, Kamiya N, Hasegawa Y, Kurasawa K, Takahashi T, et al. *Clinical features of gestational thrombocytopenia difficult to differe ntiate from immune thrombocytopenia diagnosed during pregnancy.* J Obstet Gynaecol Res, 2015. 41(1): p. 44-9.
27. Kawaguchi K, Matsubara K, Takafuta T, Shinzato I, Tanaka Y, Iwata A, et al. *Factors predictive of neonatal thrombocytopenia in pregnant women with immune thrombocytopenia.* Int J Hematol, 2014. 99(5): p. 570-6.
28. Koyama S, Tomimatsu T, Kanagawa T, Kumasawa K, Tsutsui T, Kimura T. *Reliable predictors of neonatal immune thrombocytopenia in pregnant women with idiopathic thrombocytopenic purpura.* Am J Hematol, 2012. 87(1): p. 15-21.
29. Loustau V, Debouverie O, Canoui-Poitrine F, Baili L, Khellaf M, Touboul C, et al. *Effect of pregnancy on the course of immune thrombocytopenia: a retrospective study of 118 pregnancies in 82 women.* Br J Haematol, 2014. 166(6): p. 929-35.
30. Namavar Jahromi B, Shiravani Z, and Salarian L. *Perinatal outcome of pregnancies complicated by immune thrombocytopenia.* Iran Red Crescent Med J, 2012. 14(7): p. 430-5.
31. Ozkan H, Cetinkaya M, Köksal N, Ali R, Güneş AM, Baytan B, et al. *Neonatal outcomes of pregnancy complicated by idiopathic thrombocytopenic purpura.* J Perinatol, 2010. 30(1): p. 38-44.
32. Pachi A, Carapella E, Mazzucconi MG, Gandolfo GM, Paesano R, Petrelli V, et al. *Autoimmune thrombocytopenic purpura: maternal and fetal disease.* Early Hum Dev, 1992. 29(1-3): p. 143-7.
33. Sainio S, Joutsi L, Järvenpää AL, Kekomäki R, Koistinen E, Riikonen S, et al. *Idiopathic thrombocytopenic purpura in pregnancy.* Acta Obstet Gynecol Scand, 1998. 77(3): p. 272-7.
34. Samuels P, Bussel JB, Braitman LE, Tomaski A, Druzin ML, Mennuti MT, et al. *Estimation of the risk of thrombocytopenia in the offspring of pregnant women with presumed immune thrombocytopenic purpura.* N Engl J Med, 1990. 323(4): p. 229-35.
35. Subbaiah, M. Kumar S, Roy KK, Sharma JB, Singh N, et al. *Pregnancy outcome in patients with idiopathic thrombocytopenic purpura.* Arch Gynecol Obstet, 2014. 289(2): p. 269-73.
36. Suri, V. Aggarwal N, Saxena S, Malhotra P, Varma S. *Maternal and perinatal outcome in idiopathic thrombocytopenic purpura (ITP) with pregnancy.* Acta Obstet Gynecol Scand, 2006. 85(12): p. 1430-5.
37. Valat AS, Caulier MT, Devos P, Rugeri L, Wibaut B, Vaast P, et al. *Relationships between severe neonatal thrombocytopenia and maternal characteristics in pregnancies associated with autoimmune thrombocytopenia.* Br J Haematol, 1998. 103(2): p. 397-401.
38. van der Lugt NM, van Kampen A, Walther FJ, Brand A, Lopriore E et al. *Outcome and management in neonatal thrombocytopenia due to maternal idiopathic thrombocytopenic purpura.* Vox Sang, 2013. 105(3): p. 236-43.
39. Veneri D, Franchini M, Raffaelli R.Musola M, Memmo A, FranchiM, et al. *Idiopathic thrombocytopenic purpura in pregnancy: Analysis of 43 consecutive cases followed at a single Italian institution.* Ann Hematol, 2006. 85(8): p. 552-4.

40. Wanachiwanawin W, Chansung K, Visudhiphan S, Piankijagum A. et al. *Outcomes of pregnancy in adult idiopathic thrombocytopenic purpura.* J Med Assoc Thai, 1992. 75(10): p. 584-90.
41. Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. *A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura.* Blood, 2003. 102(13): p. 4306-11.

42. Won YW, Moon W, Yun YS, Oh HS, Choi JH, Lee YY, et al. *Clinical aspects of pregnancy and delivery in patients with chronic idiopathic thrombocytopenic purpura (ITP).* Korean J Intern Med, 2005. 20(2): p. 129-34.
43. Yamada H, Kato EH, Kishida T, Negishi H, Makinoda S, Fujimoto S. et al. *Risk factors for neonatal thrombocytopenia in pregnancy complicated by idiopathic thrombocytopenic purpura.* Ann Hematol, 1998. 76(5): p. 211-4.
44. Yassaee F, Eskandari R, and. Amiri Z. *Pregnancy outcomes in women with idiopathic thrombocytopenic purpura.* Iran J Reprod Med, 2012. 10(5): p. 489-92.

**Table 1. Demographics of Women with Severe Thrombocytopaenia in Pregnancy**

| Maternal Characteristics (n = 107) | No treatment (n = 22) | Antenatal Treatment (n = 85) | P value |
|---|---|---|---|
| Maternal Age, y, [a] | 33 (19-40) | 29 (18-42) | .102 |
| Primiparous, n (%) | 8 (36) | 36 (42) | .634 |
| Singleton pregnancy, n (%) | 22 (100) | 82 (97) | 1.000 |
| Ethnicity, n (%) † | | | |
| White | 13 (59) | 60 (70.6) | .317 |
| Black | 2 (9) | 10 (11.9) | |
| Asian | 6 (27) | 10 (11.9) | |
| Other | 1 (5) | 4 (4.8) | |
| BMI, mean (SD) $kg/m^2$† | 26 (7) | 25.8 (6) | .727 |
| Smoking, n (%) | 1 (5) | 16 (19) | .184 |
| Diagnosis of ITP before pregnancy, n (%) | 15 (68) | 47 (55) | .337 |
| Age at ITP diagnosis, y, [a] | 28 (19 – 32) | 23 (2-35) | .134 |
| Lowest platelet count prior to pregnancy x $10^9/l$[a] | 19 (2-74) | 29.5 (1-119) | .178 |

[a]median (range) † 2 values missing data.

**Table 2. Labour and Delivery Management of 107 Women with Severe ITP in the UK**

| | No Rx (n=22) | Steroids (n = 38) | IVIG (n = 17) | Steroids + IVIG (n = 28) | Total (n = 107) |
|---|---|---|---|---|---|
| **Onset of Labour** | | | | | |
| Spontaneous | 5 (23) | 21 (55) | 1 (6) | 4 (14) | 32 (30) |
| Induced | 9 (41) | 8 (21) | 10 (59) | 13 (46) | 41 (38) |
| Not Reported | 0 | 0 | 1 (6) | 1 (4) | 2 (2) |
| Did not labour | 8 (36) | 9 (24) | 5 (29) | 10 (36) | 32 (30) |
| **Mode of Delivery** | | | | | |
| Caesarean Section, n, % | 9 (41) | 11 (27) | 8 (47) | 14 (50) | 42 (39) |
| Vaginal Delivery, n % | 13 (59) | 27 (73) | 9 (53) | 14 (50) | 65 (61) |
| **Fetal Blood Sampling (FBS) in labour, n (%)** | | | | | |
| Yes | 0 | 0 | 0 | 2 (11) | 2 (3) |
| No | 14 (100) | 29 (100) | 9 (75) | 16 (89) | 70 (93) |
| Not reported | 0 | 0 | 3 (25) | 0 | 3 (4) |
| **Reasons for "*no*" FBS** | | | | | |
| No indication for FBS | 11 (79) | 27 (93) | 7 (78) | 14 (88) | 60 (86) |
| Concern about low fetal platelets | 2 (14) | 1 (3.5) | 1 (11) | 1 (6) | 5 (7) |
| Maternal pyrexia | 1 (7) | 0 | 1 (11) | 0 | 2 (3) |
| Not known/reported | 0 | 1 (3.5) | 0 | 1 (6) | 3 (4) |
| **Analgesia for Vaginal Delivery** | | | | | |
| Not answered/Not known | 1 (8) | 0 | 0 | 0 | 2 (3) |
| Epidural | 2 (15) | 3 (11) | 3 (33) | 2 (14.3) | 10 (15) |
| None | 3 (23) | 7 (26) | 1 (11) | 2 (14.3) | 14 (22) |
| Opiates | 1 (8) | 10 (37) | 3 (22) | 4 (21.4) | 18 (28) |
| Entonox | 6 (46) | 7 (26) | 2 (22) | 6 (43) | 21 (32) |
| **Anaesthesia for Caesarean Section** | | | | | |
| General | 5 (56) | 7 (64) | 5 (63) | 9 (64) | 26 (62) |
| Spinal | 2 (22) | 4 (36) | 1 (13) | 4 (29) | 11 (26) |
| Epidural | 1 (11) | 0 | 2 (25) | 1 (7) | 4 (10) |
| Not known | 1 (11) | 0 | 0 | 0 | 1 (2) |
| **Lowest Recorded Platelets in Pregnancy** x $10^9$/l[a] | 31 (6-49) | 41 (5-81)* | 30 (6-55) | 21 (4-54) | 32 (4-81) |
| **Platelets at Delivery** | | | | | |
| Number Recorded, n (%) | 19 (86) | 36 (95) | 16 (94) | 24 (86) | 97 (91) |
| Platelet count at delivery, $10^9$/l[a] | 56 (14–218) | 77 (18-206) | 71 (30–152) | 62 (12 – 170) | 64 (12–218) |

[a] median (range) *One woman meeting UKOSS criteria with ITP confirmed prior to index pregnancy had a lowest recorded platelets of 148 x $10^9$/l during pregnancy, steroids were given the day before and on the day of term vaginal delivery. No maternal or neonatal complications of pregnancy or delivery were reported, but this figure has been removed from the range and is reported here as an outlier.

| Table 3. Maternal Outcomes of 105 Women with Severe ITP in the UK | | | | | |
|---|---|---|---|---|---|
| | **No Rx (n=22)** | **Steroids (n = 38)** | **IVIG (n = 17)** | **Steroids + IVIG (n = 28)** | **Total (n = 105)** |
| Epidural Haematoma, n (%) | 0 | 0 | 0 | 0 | 0 |
| Perineal Haematoma, n (%) | 0 | 0 | 0 | 0 | 0 |
| CS Wound Haematoma, n (%) | 0 | 0 | 0 | 0 | 0 |
| Estimated Blood Loss, median (range), *ml* | 500 (150–2000) | 400 (100 – 2500) | 500 (200 – 2200) | 500 (100 – 3000) | 500 (100 – 3000) |
| Postpartum Haemorrhage, n (%) | 10 (45) | 17 (45) | 9 (53) | 18 (64) | 54 (51) |
| ITU Admission ** | 0 | 0 | 0 | 0 | 0 |
| Hysterectomy due to PPH, n (%)** | 0 | 0 | 0 | 0 | 0 |
| Psychotic post-partum depression, n (%) | 0 | 1 (3) | 0 | 0 | 1 (1) |
| Death, n, (0%) | 0 | 0 | 0 | 0 | 0 |

*2 cases with other treatment reported in text. **In total cohort of 107 there was 1 ITU admission following hysterectomy (see text for detail – resistant to therapy, required azathioprine.)

| Table 4. Neonatal Outcomes for 108 infants (106 livebirths) of 105 women* with severe maternal ITP | | | | | |
|---|---|---|---|---|---|
| | **No Rx (n=22)** | **Steroids (n=39)** | **IVIg (n=19)** | **Steroids + IVIG (n=28)** | **Total (n = 108)** |
| **Miscarriage**, n (%) | 1 (4) | 0 | 0 | 0 | 1 (1) |
| **Stillbirth**, n (%) | 1 (4) | 0 | 0 | 0 | 1 (1) |
| **Birthweight (g)**[a] | 3123 (790 – 4900) | 3340 (2360-5020) | 3250 (1860 – 4135) | 3230 (2035– 3990) | 3233 (790– 5020) |
| **Cord Platelet count x $10^9$/l**[a] | 174 (59 – 350) | 212 (76 – 342) | 245 (79 – 326) | 193 (88 – 373) | 193 (59 – 373) |
| Recorded | 9 (38) | 23 (58) | 9 (47) | 17 (61) | 58 (54) |
| Not taken/No result | 15 (62) | 16 (42) | 10 (53) | 11 (39) | 52 (48) |
| **Neonatal Thrombocytopenia within First Week, n, (%)** | | | | | |
| Yes | 6 (27) | 7 (18) | 2 (11) | 8 (29) | 20 (19) |
| No | 9 (41) | 21 (54) | 13 (68) | 12 (43) | 58 (54) |
| Unknown / Not recorded | 7 (32) | 11 (28) | 4 (21) | 8 (29) | 30 (28) |
| **Platelet Nadir** | | | | | |
| <20 x $10^9$/l | 0 | 0 | 0 | 0 | 0 |
| 20-50 x $10^9$/l | 0 | 0 | 0 | 3 (11) | 3 (3) |
| 51 – 100 x $10^9$/l | 4 (18) | 2 (5) | 1 (5) | 2 (7) | 9 (8) |
| 150 – 100 x $10^9$/l | 2 (9) | 5 (13) | 1 (5) | 3 (11) | 11 (10) |
| Neonatal sepsis or other cause of thrombocytopenia, n, (%) | 0 | 1 (3) | 0 | 1 (4) | 2 (2) |
| Evidence of spontaneous recovery prior to discharge, n (%) | 6 (100) | 7 (100) | 2 (100) | 1** | 16 (100) |
| Admissions to NICU, n (%) | 0 | 2 (5) | 1(5) | 4 (15) | 7 (7) |
| Transcranial USS, n (%) | 1 (5) | 1 (3) | 0 | 0 | 2 (2) |
| Intracranial Haemorrhage, n (%) | 0 | 0 | 0 | 0 | 0 |
| Death, n (%) | 0 | 0 | 0 | 0 | 0 |

*2 pregnancies reported as case reports in text (other therapy) **Other 7 cases all discharged without therapy for thrombocytopenia but spontaneous recovery of platelet count not recorded on data collection form.