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REVIEW ARTICLE/BRIEF REVIEW

Obstetric neuraxial anesthesia at low platelet counts in the context of immune thrombocytopenia: a systematic review and meta-analysis

L'anesthésie neuraxiale obstétricale en présence d'un décompte plaquettaire bas dans le contexte d'une thrombopénie immune : une revue systématique et méta-analyse

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Abstract

Purpose *Primary immune thrombocytopenia (ITP) is an autoimmune condition affecting women of childbearing age that is characterized by diminished platelet quantity with preserved function. Although pregnant women with ITP are often denied obstetric neuraxial anesthesia (OBNA) with low platelet counts for fear of neuraxial hematoma, the true magnitude of neuraxial hematoma for ITP parturients is unknown. The aim of this systematic review and meta-analysis was to examine OBNA outcomes in ITP parturients with platelet counts below 100 x $10^9 \cdot L^{-1}$.*

Source *Articles published in MEDLINE, Embase, Web of Science, Scopus, Cochrane, and PubMed in process until May 14, 2018 were searched. Two reviewers independently screened 954 articles by title and abstract, reviewed 62 full-texts, extracted data, and assessed risk of bias for 26 articles.*

Principal findings *Of 291 pregnant women with ITP and platelet counts below 100 x $10^9 \cdot L^{-1}$, 166 received OBNA and 61 of these had platelet counts below 80 x $10^9 \cdot L^{-1}$. No neuraxial hematomas were reported. Meta-analysis of six*

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studies showed higher platelet counts in those with OBNA than without (mean difference [MD], 19 x $10^9 \cdot L^{-1}$; 95% confidence interval [CI], 11 to 26; P < 0.001), with no difference between epidural and spinal anesthesia (MD, 0.4 x $10^9 \cdot L^{-1}$; 95% CI, -4 to 4; P = 0.86).

Conclusion *Our study highlights continued reluctance to offer OBNA below the commonly quoted 80 x $10^9 \cdot L^{-1}$ platelet count, based largely on consensus and theoretical presumption of risk. This further negatively influences the accrual of large-scale data. The evidence of no neuraxial hematoma after OBNA provided herein offers support for considering neuraxial anesthesia at lower platelet count thresholds. Each patient should be afforded individualized discussion of risk and benefit relative to other analgesic measures.*

Trial registration *PROSPERO (CRD42018059220); registered 2 August, 2018.*

Résumé

Objectif *La thrombopénie immune (TPI) primaire est une maladie auto-immune qui touche les femmes en âge de procréer et se caractérise par une quantité réduite de plaquettes mais à la fonction préservée. Bien qu'on refuse souvent l'anesthésie neuraxiale obstétricale (ANOB) aux femmes enceintes atteintes de TPI ayant une numération plaquettaire réduite par peur d'un hématome neuraxial, l'incidence réelle d'hématome neuraxial chez ces parturientes est inconnue. L'objectif de cette revue systématique et méta-analyse était d'examiner les résultats d'une ANOB chez les parturientes atteintes de TPI et dont le décompte plaquettaire était inférieur à 100 x $10^9 \cdot L^{-1}$.*

Source *Nous avons effectué des recherches dans les articles publiés dans les bases de données MEDLINE, Embase, Web of Science, Scopus, Cochrane et PubMed jusqu'au 14 mai 2018. Deux réviseurs ont présélectionné de façon indépendante 954 articles en fonction de leur titre et de leur résumé, passé en revue 62 textes intégraux, extrait des données et évalué le risque de biais de 26 articles.*

Constatations principales *Sur 291 femmes atteintes de TPI et dont le décompte plaquettaire était inférieur à 100 x $10^9 \cdot L^{-1}$, 166 patientes ont reçu une ANOB et 61 de ces femmes avaient une numération plaquettaire inférieure à 80 x $10^9 \cdot L^{-1}$. Aucun hématome neuraxial n'a été rapporté. La méta-analyse de six études a identifié un décompte plaquettaire plus élevé chez les femmes ayant reçu une ANOB que chez celles n'en ayant pas reçu (différence moyenne [DM], 19 x $10^9 \cdot L^{-1}$; intervalle de confiance [IC] 95 %, 11 à 26; P < 0,001), aucune différence n'ayant été observée entre les femmes ayant reçu une anesthésie péridurale vs rachidienne (DM, 0,4 x $10^9 \cdot L^{-1}$; IC 95 %, -4 à 4; P = 0,86).*

Conclusion *Notre étude souligne la réticence persistante à offrir une ANOB si le décompte plaquettaire fréquemment cité de 80 x $10^9 \cdot L^{-1}$ n'est pas atteint, réticence principalement fondée sur le consensus et la présomption théorique d'un risque. En outre, cela influence négativement l'accumulation de données à grande échelle. Les données probantes d'absence d'hématome neuraxial après une ANOB présentées ici soutiennent la proposition d'envisager une anesthésie neuraxiale à des seuils de décompte plaquettaire plus bas. Chaque patiente devait pouvoir bénéficier d'une discussion personnalisée quant aux risques et aux bienfaits de cette modalité par rapport aux autres modalités analgésiques.*

Enregistrement de l'étude *PROSPERO (CRD42018059220); enregistrée le 2 août 2018.*

Primary immune thrombocytopenia purpura (ITP) is an autoimmune condition marked by increased platelet destruction, which is mediated by T-cells and anti-platelet glycoprotein antibodies. It affects around 1–2/1,000 pregnancies.[1] Most pregnant women with ITP are asymptomatic, but others may experience easy bruising, petechiae, epistaxis, or mucosal bleeding.[2] ITP is characterized by platelet counts < 100 x $10^9 \cdot L^{-1}$ with exclusion of other potential etiologies, and may initially present pre-conception or during the antenatal period.[3]

Current obstetric pain management is mostly reliant on neuraxial anesthesia, which collectively refers to epidural, spinal, and combined-spinal epidural (CSE) techniques, given their excellent tolerability and superior level of pain control.[4] Some guidelines quote "normal risk" of OBNA for patients with ITP at platelet counts > 75 x $10^9 \cdot L^{-1}$ and "increased risk" at platelet counts of 50–75 x $10^9 \cdot L^{-1}$.[5] Others suggest that OBNA is acceptable at platelet counts > 70 x $10^9 \cdot L^{-1}$ in most cases and may be acceptable at lower platelet counts under individual circumstances.[6] Many also acknowledge that a platelet count cut-off predictive of OBNA complications has not been established.[7]

While thrombocytopenic conditions carry an increased risk of bleeding, warranting careful evaluation prior to consideration of neuraxial anesthesia, this risk varies depending on the underlying pathophysiology.[8,9] Specifically, hypertensive disorders of pregnancy are characterized by platelet dysfunction,[10] but although ITP involves accelerated platelet destruction, the function of the remaining platelets typically remains intact.[11,12]

Studies to date have suggested that the risk of neuraxial hematoma in the general obstetric setting is lower than in the non-obstetric population. Following epidural

placement, the risk of neuraxial hematoma in the obstetric population was estimated by Ruppen *et al.* to be 1:168,000.[13] Similarly, Moen *et al*. found it to be 1:200,000 in obstetric patients, compared with 1:3,600 in non-obstetric female patients undergoing knee arthroplasty and 1:29,000 in non-obstetric female patients undergoing hip arthroplasty.[14] Comparably, Ehrenfeld *et al*. reported the risk of epidural hematoma in the non-obstetric population to be approximately 1:7,246.[15] Following spinal anesthesia, the risk of neuraxial hematoma was estimated by Moen *et al*. at 1:50,000 in the obstetric population and 1:22,000 in female patients undergoing surgery for a hip fracture.[14] In a comprehensive literature review, neuraxial hematoma complicated 13/850,000 epidural anesthetics and 7/650,000 spinal anesthetics in the general population, suggesting an incidence of neuraxial hematoma of $< 1{:}150{,}000$ and $< 1{:}220{,}000$ for epidural and spinal anesthesia respectively.[16]

Nevertheless, citing concerns regarding increased bleeding risk at lower platelet counts and fearing the development of a neuraxial hematoma with its potential for irreversible neurologic injury, many anesthetists are reluctant to perform OBNA at platelet counts below 70–80 x $10^9 \cdot L^{-1}$, and practice varies widely among centres.[17] Owing to the rarity of the condition, the specific platelet count predictive of complications related to neuraxial anesthesia has not been determined,[7] yet many pregnant women with ITP and intermediately low platelet counts (50–75 x $10^9 \cdot L^{-1}$) are denied access to OBNA, resulting in suboptimal pain control, a situation typically unacceptable in other areas of medicine.[18]

Previous reviews have examined the outcomes of thrombocytopenic parturients following neuraxial anesthesia,[19-21] but none have specifically addressed OBNA outcomes in the context of primary ITP. Given the typically preserved platelet function associated with ITP, lower platelet counts at placement of OBNA may be safer than in other thrombocytopenic conditions. Thus, in this systematic review and meta-analysis we aimed to include randomized-controlled trials, controlled trials, observational studies, and case reports of pregnant women with ITP in the thrombocytopenic range to: i) describe the incidence of neuraxial hematoma or neurologic complications in those who received OBNA; ii) examine whether there was a difference in platelet counts in those who received OBNA compared with those who did not; iii) evaluate whether there was a difference in platelet counts at time of placement of OBNA in the form of epidural anesthesia compared with spinal anesthesia.

Methods

The study protocol was registered with PROSPERO[22] (CRD42018059220), conducted according to PRISMA guidelines,[23] and reported following the MOOSE guidelines.[24]

Data sources and searches

A comprehensive electronic search strategy was developed and executed by an experienced librarian (D.H.) and is available in the Appendix. The strategy was initially developed for MEDLINE and peer-reviewed by A.K.M. prior to translation for use in the remaining databases. Examples of key words used for the database searches are: "idiopathic and/or immune thrombocytopenia", "platelet count", "anesthesia", "epidural", "spinal", "regional", "neuraxial", "obstetric", "pregnancy", "pregnant women", "complications", and their derivatives (Appendix). The literature search was performed in MEDLINE, EMBASE, Web of Science, Scopus, the Cochrane Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews, as well as the PubMed in process platform, including all articles indexed until May 14, 2018. The search was limited to human data, without restriction to publication year or language. All references obtained from the search were imported into EndNote (X7.5.1.1). Reference lists of included articles were manually scanned for additional relevant studies.

Study selection

Studies were included if they i) involved pregnant women with a current or previous diagnosis of primary ITP; ii) reported on peripartum neuraxial anesthesia for labour and delivery consisting of an epidural, spinal, or CSE; iii) represented randomized-controlled trials, controlled trials, observational studies, and case reports; and iv) reported on at least one of the pre-specified primary outcomes. The primary outcomes included: a) hemorrhagic complications (epidural or spinal hematoma), and b) neurologic complications (paresis or paraplegia, either transient or permanent). To avoid duplicating data, only the most recent publication featuring the same patient population was included.

Studies investigating other causes of thrombocytopenia (i.e., hereditary thrombocytopenic syndromes, hypertensive disorders of pregnancy, thrombotic thrombocytopenic

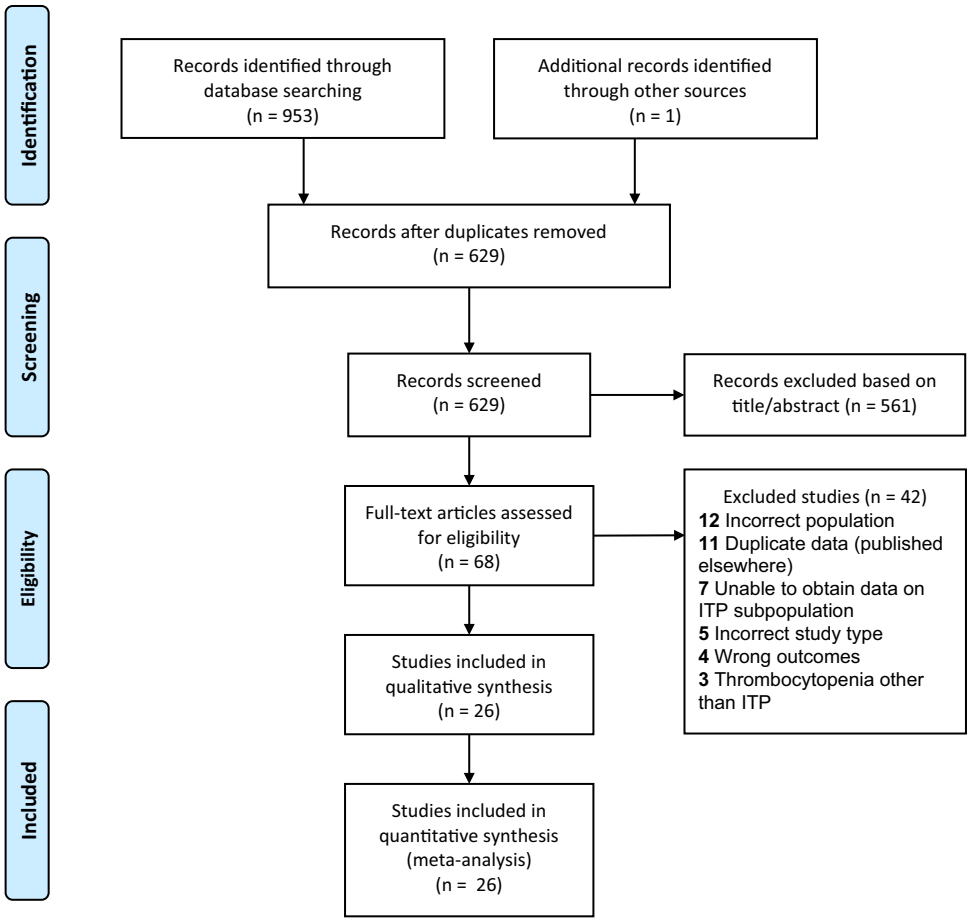

Fig. 1 PRISMA diagram of search results for platelet counts at the time of obstetric neuraxial anesthesia placement in pregnancies complicated by immune thrombocytopenia

purpura, gestational thrombocytopenia, etc.) were excluded, as were reviews, commentaries, and letters to the editor not containing original data. Title and abstract screening was conducted independently by two reviewers (L.J.B. and A.K.M.), and disagreement was resolved by discussion and consensus.

Data extraction and quality assessment

Data were extracted and analyzed independently by two reviewers (L.J.B. and A.K.M.) to a case report form, which was pilot-tested on five of the included studies selected at random, and amended as appropriate. Where feasible, the pre-and post-procedure platelet counts, needle gauge/type used for the block, difficulties during insertion/placement, and treatment preceding the procedure were recorded. Disagreement was resolved by discussion and consensus. Original study authors were contacted for further information where required. Within studies assessing multiple etiologies of thrombocytopenia, data on the ITP population only were abstracted.

Risk of bias was assessed according to the Newcastle-Ottawa Scale for Cohort Studies,[25] the National Institute of Health's National Heart, Lung, and Blood Institute (NHLBI) Quality Appraisal Tool for Case Series,[26] and the Joanna Briggs Institute's Checklist for Case Reports[27] as appropriate. While, strictly speaking, the risk of bias cannot be assessed in case reports, this tool is meant to ensure that case reports are critiqued according to the tool's criteria and that only those with sufficient detail are included. Once all entries were complete, both researchers (L.J.B. and A.K.M.) reviewed the files and any disagreement was resolved by discussion until consensus was achieved.

Statistical analysis

Data were grouped according to study design and summarized in tabular format. Studies including individuals with various types of thrombocytopenia including ITP, where specific types of OBNA were provided to one or two individuals with ITP, were analyzed alongside case reports regardless of the original study design. Continuous data were extracted as a mean (standard deviation [SD]) or median (interquartile range [IQR]). IBM SPSS Statistics for Mac, v.25 (IBM Corp., Armonk, NY, USA) was used to perform data management and statistical analyses. When quantitative analysis was not

Table 1 Characteristics and risk of bias assessment for case series and case reports on neuraxial anesthesia in pregnant women with ITP

Cohort Studies											
Author Year Country Setting Single *vs.* multicentre	Years of study	Design	Number of ITP-affected deliveries with available platelet counts	Inclusion criteria	Exclusion criteria	Type (number) of OBNA	ITP Tx	Needle gauge/type	Risk of bias assessment (NOS)		
									Selection comparability outcome ★★★★ ★★ ★★★	Total /9	RoB 1–3: High 4–6: Moderate 7–9: Low
Deruddre 2007 France Tertiary care Single centre	Nov 1995 Feb 2000	RC	52	1) Isolated thrombocytopenia; 2) absence of alternate cause (e.g., HIV, SLE, congenital, etc.); 3) presence of anti-PLT antibodies &/or exclusion of other causes of thrombocytopenia; 4) birth of child with low PLTs & no known etiology. ITP diagnosis = 1 & 2 plus 3 or 4.	NR	Unspecified OBNA (19)	Tx reported for entire cohort (no details for OBNA) CS 19 (36%) IVIG 2 (4%) CS±IVIG 8 (15%) None 22 (42%)	NR	★★★★ - ★★★	7	Low
Care 2018 United States Tertiary care Multicentre	Jun 2013 Jan 2015	PC	26	Pregnant women with severe antenatal ITP (clinically & by platelet count < 50*), with other causes excluded (i.e., HDP, AFLP, APS, hereditary thrombocytopenia); pregnant women with isolated thrombocytopenia with clinical decision to treat prior to delivery	Secondary ITP (i.e., SLE, HCV, CMV, HIV, etc.) Authors felt above criteria would exclude cases of GT (given rarity of GT with PLTs < 50)	Epidural (14) Spinal (12)	CS 7 (27%) Epidural 3 Spinal 4 IVIG 5 (19%) Epidural 4 Spinal 1 CS+IVIG 7 (27%) Epidural 3 Spinal 4 Other++ 3 (12%) Epidural 1 Spinal 2 None 4 (15%) Epidural 3 Spinal 1	NR	★★★ - ★★★	6	Moderate

Table 1 continued

Retrospective/Prospective Case Series									
Author Year Country	Years of study	Number of ITP-affected deliveries with available platelet counts	Timing of diagnosis	Inclusion criteria	Exclusion criteria	Type (number) of OBNA	ITP Tx	Needle and catheter gauge/type	Risk of bias (Good Fair Poor)
Rasmus 1989 Spain	1988	1	PP	Admitted for delivery with antenatal or post-partum PLTs < 100	NR	Epidural (1)+	None	17G Tuohy needle 19G epidural catheter	Fair
Beilin 1997 USA	1993–1996	12	NR	Women with peripartum PLTs < 100	NR	Epidural (6)	NR	18G Hustead needle 20G multiorifice catheter	Fair
Webert 2003 Canada	Jan 1999–Dec 2000	42	Pre-preg AP	Pregnancy with history of thrombocytopenia & other causes (i.e., HDP, DIC, drug-induced, SLE, TTP, HUS, hereditary thrombocytopenia) excluded	GT (PLT > 70 in asymptomatic patients) or low PLTs associated with HDP	Epidural (42)	Tx unclear 1 (2%) – PLTs < 50 (epidural) None 41 (98%) – PLTs > 50	NR	Good
Ramos 2004 Spain	1993–2003	28	Pre-preg AP	Pregnant women with ITP after exclusion of other causes of thrombocytopenia	NR	Epidural (10) Spinal (7)	Tx reported for entire cohort (no details for OBNA) CS 14 (50%) CS+IVIG 1(4%) None 13 (46%)	NR	Fair
Tanaka** 2009 Canada	April 2001–March 2006	19	NR	PLTs < 100 on the day of anesthesia	Preeclampsia, hypertension	Epidural (7) Spinal (5)	NR	NR	Fair
Tay^ 2014 UK	2008–2012	32	Pre-preg AP	Thrombocytopenia (PLTs < 100) in pregnancy	Obstetric and non-obstetric causes of thrombocytopenia other than ITP	Epidural (3) Spinal (5) CSE (2)+	CS 9 (28%) Spinal 1 CSE 1 No OBNA 7 IVIG 2 (6%) No OBNA 2 CS+IVIG 1(3%) No OBNA 1 Other+++ 2 (6%) No OBNA 2 None 18 (56%) Epidural 3 Spinal 4 CSE 1 No OBNA 10	NR	Fair

Table 1 continued

Retrospective/Prospective Case Series									
Author Year Country	Years of study	Number of ITP-affected deliveries with available platelet counts	Timing of diagnosis	Inclusion criteria	Exclusion criteria	Type (number) of OBNA	ITP Tx	Needle and catheter gauge/type	Risk of bias (Good Fair Poor)
Goodier 2015 USA	Jan 1997–Dec 2007	28	NR	Admitted for delivery with a PLTs < 100	NR	Epidural (8) Spinal (7) No OBNA (13)	CS Tx of "several" individuals in each group. Number of cases per group not reported PLT Transfusion Epidural 0 Spinal 0 No OBNA 5/13	NR	Good
Lee 2017 USA	2004–2015	25	NR	Obstetric patients with PTLs < 100 within 72h of OBNA	PLT count > 100, underlying coagulopathy, or antiplatelet medication	Epidural (17) Spinal (7) CSE (1)$^{+}$	NR	NR	Good
Malinowski 2017 Canada	Jan 2000–Aug 2014	234	Pre-preg AP	History of thrombocytopenia (PLTs < 100) pre-dating pregnancy or with onset in first trimester	Thrombocytopenia other than ITP, (i.e., HDP, sepsis); PLTs > 70 that normalized PP & lack of history of low PLTs outside pregnancy	Epidural (96) Spinal (40)	CS 42 (18%) Epidural 24 Spinal 5 No OBNA 13 IVIG 30 (13%) Epidural 8 Spinal 3 No OBNA 19 CS+IVIG 25 (11%) Epidural 5 Spinal 4 No OBNA 16 None 137 (59%) Epidural 59 Spinal 28 No OBNA 50	NR	Good

Table 1 continued

Retrospective/Prospective Case Series									
Author Year Country	Years of study	Number of ITP-affected deliveries with available platelet counts	Timing of diagnosis	Inclusion criteria	Exclusion criteria	Type (number) of OBNA	ITP Tx	Needle and catheter gauge/type	Risk of bias (Good Fair Poor)
Comont 2017 France	2010–2015	2	Pre-preg	Women with primary ITP, in complete remission for at least 5 years without treatment at pregnancy onset	Women with secondary ITP (APS, immunodeficiency, chronic viral infection, etc); GT or other causes of low PLTs (HDP, AFLP)	Epidural (1)$^{+}$	IVIG No OBNA 1/1 CS+IVIG Epidural 1/1	NR	Fair
Alkholany^ 2017 UK	2012–2013	25	NR	Obstetric patients with AP thrombocytopenia	NR	Epidural (2)$^{+}$ Spinal (5)	CS Epidural 1/2 Otherwise NR	NR	Fair
Wegnelius 2018 Sweden	Jun 2007 Nov 2011	75	Pre-preg AP	All pregnant women with ITP	GT, low PLTs of alternate cause (i.e., HDP)	Epidural (10) Spinal (10)	CS 6 (8%) Epidural 2 No OBNA 4 IVIG 13 (17%) No OBNA 13 CS+IVIG 9 (12%) Epidural 1 Spinal 2 No OBNA 6 None 47 (63%) Epidural 7 Spinal 8 No OBNA 32	NR	Good
Levy 2018 Israel	Jan 2011 Dec 2014	8	NR	All women with PLTs < 100 admitted for delivery	Confirmed manual PLTs > 99	Epidural (4) Spinal (2)$^{+}$	CS 6 (75%) Epidural 3 Spinal 2 No OBNA 1 None 2 (25%) Epid 1 No OBNA 1	18G Tuohy for epidural 26G pencil point (spinal)	Good

Table 1 continued

RETROSPECTIVE/PROSPECTIVE CASE SERIES

Author Year Country	Years of study	Number of ITP-affected deliveries with available platelet counts	Timing of diagnosis	Inclusion criteria	Exclusion criteria	Type (number) of OBNA	ITP Tx	Needle and catheter gauge/type	Risk of bias (Good Fair Poor)
Gilmore 2018 New Zealand	July 2013 July 2016	28	Pre-preg AP	Pregnant women who attended maternity services or the intensive care unit; PLTs < 100	Thrombocytopenia other than ITP (i.e., hematologic disorder, autoimmune, DIC, AFLP HDP), GT (with new low PLTs in pregnancy but > 70 and normal PLTs outside pregnancy)	Epidural (19) Spinal (7) CSE (2)$^{+}$	CS 4 (14%) Epidural 4 CS+IVIG 2(7%) Epidural 1 Spinal 1 None 22 (79%) Epidural 14 Spinal 6 CSE 2	16G Tuohy (epidural) 25G B-Braun (spinal)*** 27G pencil point (CSE)	Good

CASE REPORTS

Author Year Country	Years of study	Number of ITP-affected deliveries with available platelet counts	Timing of diagnosis	Type (number) of OBNA	Needle and catheter gauge/type	Difficulties	ITP treatment	RoB assessment *(Include Exclude)*
Hew-Wing 1989 Canada	1989	1	PP	Epidural	NR	None: catheter introduced on 1st attempt, passed into epidural space (L4–5) w/o paresthesia and no blood or CSF was seen	None	Include
Steer 1993 USA	1993	1	Pre-preg	Epidural	NR	NR	None	Include
Mardirosoff 1998 Belgium	1997	1	Pre-preg	Spinal	27G Whitacre needle	None	None	Include
Campos 1998 USA	1998	1	NR	CSE	16G Tuohy needle 27G spinal needle	None	CS	Include
Cook 1999 UK	1999	1	NR	Epidural	NR	None	None	Include

Table 1 continued

Case Reports								
Author Year Country	Years of study	Number of ITP-affected deliveries with available platelet counts	Timing of diagnosis	Type (number) of OBNA	Needle and catheter gauge/type	Difficulties	ITP treatment	RoB assessment *(Include Exclude)*
Moeller-Bertram 2004 USA	2004	1	Pre-preg (undisclosed)	Epidural	18G Tuohy-Schliff needle 20G multi-orifice catheter	Persistent bleeding from puncture site during dressing placement ceased spontaneously within 5–6 min; bleeding at puncture site during removal controlled with pressure	None	Include
Ibrahim^ 2009 Egypt	2009	1	AP	CSE	16G Tuohy 27G spinal needle	Bleeding at injection site during removal of catheter; stopped with pressure for 7 min	NR	Include
Schuitemaker Requena^ 2010 Venezuela	2010	1	Pre-preg	Epidural	NR	NR	None	Include
Dalela^ 2016 USA	2016	1	NS	Epidural	NR	Inadvertent dural tap with 1st attempt at epidural catheter placement; intrathecal catheter placed instead	PLTs	Include
Byrne^ (2017) Ireland	2017	1	Antenatally	Epidural	NR	NR	CS + IVIG + rituximab + azathioprine	Include

AFLP = acute fatty liver of pregnancy; AP = antepartum; APS = antiphospholipid syndrome; CS = corticosteroids; CSE = combined spinal epidural; DIC = disseminated intravascular coagulation; G = gauge; GT = gestational thrombocytopenia; HDP = hypertensive disorder of pregnancy; HUS = hemolytic uremic syndrome; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin; N/A = not available; NOS = New-Castle Ottawa Scale; NR = not reported; OBNA = obstetric neuraxial anesthesia; PLT = platelet; Pre-preg = pre-pregnancy; PP = postpartum; PC = prospective cohort; RC = retrospective cohort; RoB = risk of bias; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura; Tx = treatment

[+] Original publication is a retrospective case-series; however, it was analyzed alongside case reports because only one individual had ITP

*Platelet counts x $10^9 \cdot L^{-1}$

**Only cases unaccounted for in Malinowski *et al.* reported here

*** Single pass but bloody tap with one spinal, otherwise no difficulties with placement reported in any cases

^Abstract or conference proceeding

[++] For epidural, other indicates unspecified (n=1), for spinal other indicates anti-D and platelets (n=1), and platelets (n=1)

[+++] Other indicates CS + Anti-D (n=1), IVIG + Anti-D (n=1)

possible, such as in the case of non-numerical outcomes or inconsistency in reporting across studies, data were presented in narrative format.

For the subset of studies reporting individual platelet counts $< 100 \times 10^9 \cdot L^{-1}$ and OBNA, a meta-analysis of difference in platelet count means with respect to anesthetic modality was conducted. As the variables were continuous, the mean difference (MD) was calculated. A random-effects model was chosen given the diversity of individual studies.[28] The degree of heterogeneity across the studies was examined using I^2 values,[29] classifying 50% as moderate heterogeneity and 75% as high heterogeneity. A P value of < 0.05 was considered statistically significant. Review Manager software (version 5.3; the Cochrane Collaboration, Oxford, United Kingdom) was used to complete the meta-analysis.

Results

Figure 1 shows the PRISMA flow diagram detailing study selection. A total of 26 studies met predefined inclusion criteria: two cohort studies,[30,31] 14 case series,[17,18,20,32-42] and ten case reports.[43-52] Individual patient data were available or obtained from original study authors for nine of these studies. No randomized-controlled trials on OBNA outcomes in ITP patients were identified.

Risk of bias assessment

The risk of bias assessment is described in Table 1. Risk of bias according to the Newcastle-Ottawa Scale for Cohort Studies[25] was low in one cohort study and moderate in the other cohort study. Using the NHLIB Quality Appraisal Tool for Case Series,[26] seven studies were assessed to be of good quality and seven were rated as fair. The deficiencies were mainly owing to incomplete descriptions of the anesthetic intervention. All ten case reports were considered of satisfactory quality to merit inclusion based on the Joanna Briggs Institute Checklist for Case Reports.[27]

Description of study characteristics

Study characteristics are presented in Table 1. Platelet counts at delivery were available for 647 ITP-affected pregnancies. Of these, OBNA was initiated in 381 pregnancies: 247 epidurals, 109 spinals, six CSEs, and 19 unspecified OBNA. Across studies, 15–98% of patients did not receive platelet-enhancing treatment, and where treatment was administered, the majority received corticosteroids, intravenous immunoglobulin, or a combination of these agents (Table 1). Data related to the needle gauge and type used for OBNA were inconsistently recorded. Where reported, needles for epidural placement included 16–18G Tuohy (an 18G Hustead needle was used in one instance), needles for spinal placement were 25–26G, with an atraumatic tip. Difficulties during placement of OBNA were only discussed in seven case reports: no difficulties in four,[44,45,47,49] persistent bleeding from the puncture site managed with pressure in two,[48,50] and an inadvertent dural tap in one (Table 1).[46]

Pre-OBNA platelet counts and outcomes

Aggregate, study-specific, pre-OBNA platelet counts for all 647 pregnancies, 381 of which received OBNA, are available as Electronic Supplementary Material (eTable). Given concerns surrounding potential OBNA-related complications at platelet counts in the thrombocytopenic range, our further analysis focuses on the sub-population of pregnancies with pre-OBNA platelet counts below $100 \times 10^9 \cdot L^{-1}$. Of 345 pregnancies within this subset, 205 received OBNA, and their respective pre-OBNA platelet counts are shown in Table 2.

Individual patient data were available/obtained for nine studies[17,18,20,30,32,35,36,39,40] and 17 case reports,[20,32,34-36,38,40,43-52] representing 291 pregnancies with pre-OBNA platelet counts below $100 \times 10^9 \cdot L^{-1}$ for which OBNA was administered in 166 pregnancies, as well as 160 pregnancies with pre-OBNA platelet counts below $80 \times 10^9 \cdot L^{-1}$ for which OBNA was administered in 60 pregnancies (Table 3). The frequency of OBNA placement at progressively lower platelet count categories is shown in Fig. 2.

With respect to the primary outcomes, no neuraxial hematomas or neurologic complications were reported in any of the included studies.

In the absence of reported events, we calculated the theoretical upper limit of the 95% confidence interval (CI) for neuraxial hematoma using the "rule of 3" ($R=3/n$), where R represents the upper bound of the 95% CI for maximum risk of a selected outcome, and n represents the number of individuals without the outcome of interest.[53] This technique uses probability theory and the characteristics of the binomial distribution to estimate the maximum rate of events when zero events are reported among n observations. Based on the individual data gathered in our study, we estimate that the upper bound of the 95% CI for the risk of neuraxial hematoma is 1.8% ($3/n = 3/166$) in individuals with platelet counts below $100 \times 10^9 \cdot L^{-1}$, 4.8% (3/60) in individuals with platelet counts below $80 \times 10^9 \cdot L^{-1}$, and 8.4% (3/34) in individuals with platelet counts below $70 \times 10^9 \cdot L^{-1}$.

Table 2 Aggregate platelet counts prior to obstetric neuraxial anesthesia in ITP patients with platelet counts below 100 x $10^9 \cdot L^{-1}$

Platelet counts prior to placement of neuraxial anesthesia in ITP patients with platelet counts < 100*					
Type of neuraxial anesthesia	Study	*n*	Mean (SD)	Median [IQR]	Range
Epidural	Care	8	65 (31)	75 [38–92]	14–94
	Beilin	3			92–96
	Webert	26			< 50 (*n*=1)
					50–75 (*n*=6)
					76–100 (*n*=19)
	Ramos	5			70–100
	Tanaka	7	89 (± 14)	97 [79–99]	63–99
	Tay	3	90 (± 3)	90 [87–xx]	87–93
	Goodier	8	83 (±13)	81 [71–97]	66–98
	Lee	17	85 (± 11)	89 [80–93]	54–98
	Malinowski	40	79 (12)	82 [69–86]	45–98
	Levy	4	82 (± 2)	81 [80–84]	80–84
	Gilmore	12	86 (9)	87 [79–94]	70–99
	Case Reports^	7	52 (14)	72 [18–81]	2–95
Spinal	Care	7	75 (25)	85 [67–92]	23–93
	Ramos	5			70–100
	Tanaka	5	87 (± 9)	83 [79–97]	78–97
	Tay	5	88 (± 6)	86 [84–94]	83–97
	Goodier	7	80 (±19)	88 [57–99]	52–99
	Lee	7	82 (±22)	89 [86–93]	34–97
	Malinowski	15	78 (14)	82 [67–97]	48–99
	Alkholany	3	85 (8)	80 [80–xx]	80–94
	Gilmore	2	92 (6)	92 [88– xx]	88–96
	Case Reports^^	4	63 (13)	66 [50–73]	45–75
CSE	Case Reports^^^	5	75 (7)	76 [63–88]	50–88
Unexposed (No OBNA)	Beilin	6			28–80
	Ramos	9			< 50 (*n*=5)
					50–70 (*n*=2)
					71–100 (*n*=2)
	Tanaka	7	62 (7)	65 [48–79]	27–81
	Tay	17	75 (5)	87 [63–93]	35–99
	Goodier	13	56 (5)	53 [43–69]	34–95
	Malinowski	81	56 (2)	56 [42–70]	20–99
	Alkholany	5	85 (6)	93 [72–95]	63–96
	Levy	2	48 (32)	48 [16–xx]	16–79

* Platelet counts x $10^9 \cdot L^{-1}$

^ Case reports for epidural consist of: Hew-Wing, Rasmus, Steer, Cook, Moeller-Bertram, Schuitemaker Requena, Dalela

^^ Case reports for spinal consist of: Mardirosoff, Campos, Levy

^^^ Case Reports for CSE consist of: Ibrahim, Tay, Lee, and Gilmore

CSE = combined spinal epidural; IQR = interquartile range; OBNA = obstetric neuraxial anesthesia

In a meta-analysis of six studies, platelet counts were higher in those with OBNA than those without (MD, 19 x $10^9 \cdot L^{-1}$; 95% CI, 11 to 26; $P < 0.00001$) (Fig. 3A), but did not differ between epidural and spinal anesthesia (MD, 0.4 x $10^9 \cdot L^{-1}$; 95% CI, -4 to 4; $P = 0.86$) (Fig. 3B).

Discussion

This is the first systematic review to analyze platelet counts prior to OBNA solely in patients with ITP, excluding other thrombocytopenic conditions, and to provide patient-level

Table 3 Platelet counts based on individual data for sub-population of patients with pre-OBNA platelet counts below 100 x $10^9 \cdot L^{-1}$ and below 80 x $10^9 \cdot L^{-1}$

Modality	Measure	Platelet counts < 100 (x $10^9 \cdot L^{-1}$)				Platelet counts < 80 (x $10^9 \cdot L^{-1}$)			
		Including CR		Excluding CR		Including CR		Excluding CR	
Epidural	Mean	*n*=106	79	*n*=99	81	*n*=38	62	*n*=33	65
	(SD)		(18)		(15)		(19)		(14)
	Median		83		84		68		69
	[IQR]		[72–91]		[75–92]		[61–74]		[63–75]
	Range		2–99		14–99		2–79		14–79
Spinal	Mean	*n*=55	80	*n*=51	81	*n*=19	62	*n*=15	62
	(SD)		(17)		(16)		(16)		(17)
	Median		84		85		67		67
	[IQR]		[73–91]		[77–92]		[52–75]		[52–75]
	Range		23–99		23–99		23–79		23–79
CSE	Mean	*n*=5	75	*n*=0	n/a	*n*=3	67	*n*=0	n/a
	(SD)		(16)				(15)		
	Median		76		n/a		75		n/a
	[IQR]		[63–88]				[50–xx]		
	Range		50–88		n/a		50–76		n/a
Unexposed	Mean	*n*=125	60			*n*=100	53		
(no CRs)	(SD)		(21)				(16)		
	Median		60				54		
	[IQR]		[45–74]				[41–66]		
	Range		16–99				16–79		

CR = case report; CSE = continuous spinal-epidural; IQR = interquartile range; OBNA = obstetric neuraxial anesthesia; SD = standard deviation

analysis. Our results show that the mean and median platelet counts for placement of neuraxial anesthesia in this setting are consistently in the mid 80 x $10^9 \cdot L^{-1}$; however, 60 instances of neuraxial anesthesia placement without complications at values progressively lower than 80 x $10^9 \cdot L^{-1}$ have been reported. Specifically, based on the subset of studies for which individual data were available for patients with platelet counts below 80 x $10^9 \cdot L^{-1}$, OBNA was placed at platelet counts 70–79 x $10^9 \cdot L^{-1}$ in 26 (43%), 60–69 x $10^9 \cdot L^{-1}$ in 17 (28%), 50–59 x $10^9 \cdot L^{-1}$ in six (10%), and below 50 x $10^9 \cdot L^{-1}$ in 11 (18%) cases. Not surprisingly, a meta-analysis of the six studies containing a comparator group showed a significant MD in platelet counts between the group that received OBNA and the group that did not. As spinal anesthesia typically involves a "single-shot" approach with a smaller needle than that used for an epidural,[54] there is typically a greater comfort level with this approach at lower platelet counts. Interestingly, our meta-analysis did not demonstrate a difference in the mean platelet counts between the group that received epidural and the group that received spinal anesthesia.

The systematic review was undertaken owing to our observations that many women with ITP are denied OBNA because of concerns over the potential, though largely theoretical, risk of neuraxial hematoma and its neurologic sequelae. The reluctance to provide neuraxial anesthesia, and fear of this complication, stems from the perception of an increased bleeding risk at platelet counts in the thrombocytopenic range. Nevertheless, there is no direct compelling evidence in the literature substantiating excessive bleeding in individuals with ITP with non-severe thrombocytopenia (platelets > 50 x $10^9 \cdot L^{-1}$)[55] during hemostatic challenges such as childbirth or surgery.[31,42,56] A cohort study comparing maternal outcomes between 46 women with ITP with platelet counts above 100 × 10^9 L^{-1} (range 101–378 × 10^9 L^{-1}) with those below 100 × $10^9 \cdot L^{-1}$ (range 61–98 × 10^9 L^{-1}) found no difference in estimated blood loss at Cesarean delivery, and no differences in incidence of wound complications or need for transfusion.[56] Deruddre *et al.* echoed these findings, reporting postpartum hemorrhage in 3/20 deliveries in the non-thrombocytopenic group compared with 1/32 deliveries in the thrombocytopenic group, and further documenting that all cases resulted from either retained placenta or uterine atony.[31] In the study by Webert *et al.*, none of the 17 women with platelet counts below 50 x $10^9 \cdot L^{-1}$ experienced significant peripartum bleeding.[41] The lack of association with excessive bleeding

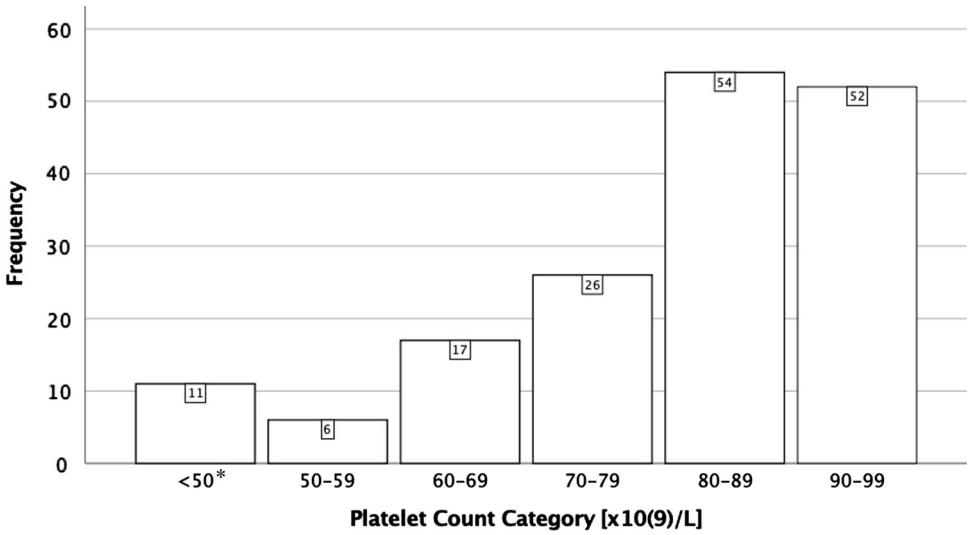

Fig. 2 Frequency of obstetric neuraxial anesthesia placement at progressively lower platelet count categories; 166/291 patients with platelet counts below 100 x $10^9 \cdot L^{-1}$ and 60/160 patients with platelet counts < 80 x $10^9 \cdot L^{-1}$ received obstetric neuraxial anesthesia. * Within the category of platelet count <50 x 109·L-1, seven epidurals were placed at platelet counts of 2, 14, 18, 26, 36, 43, and 45 x 109·L-1 and four spinals were placed at platelet counts of 23, 34, 45, and 48 x $10^9 \cdot L^{-1}$

in ITP in the thrombocytopenic range presumably stems from the fact that platelet function in ITP remains preserved,[11,12,57] unlike other thrombocytopenic syndromes encountered in pregnancy such as preeclampsia/hemolysis, elevated liver enzymes, and low platelets (HELLP), or inherited bleeding disorders, which have altered platelet function.[8-10]

No adverse events, including neuraxial hematoma or neurologic compromise, were reported in any of the studies comprising our systematic review. Indeed, within the existing literature, the only reports of a neuraxial hematoma affecting obstetric patients occurred in the setting of an underlying coagulopathy, namely hemophilia, which was undiagnosed at the time of neuraxial anesthesia placement,[19] and severe HELLP syndrome.[14] This in itself is worth considering, as typically by virtue of publication bias, case reports tend to over-represent the occurrence of adverse outcomes. The literature does not contain any reports of neuraxial hematoma in the context of ITP. Moreover, the risk of epidural hematoma overall is lower

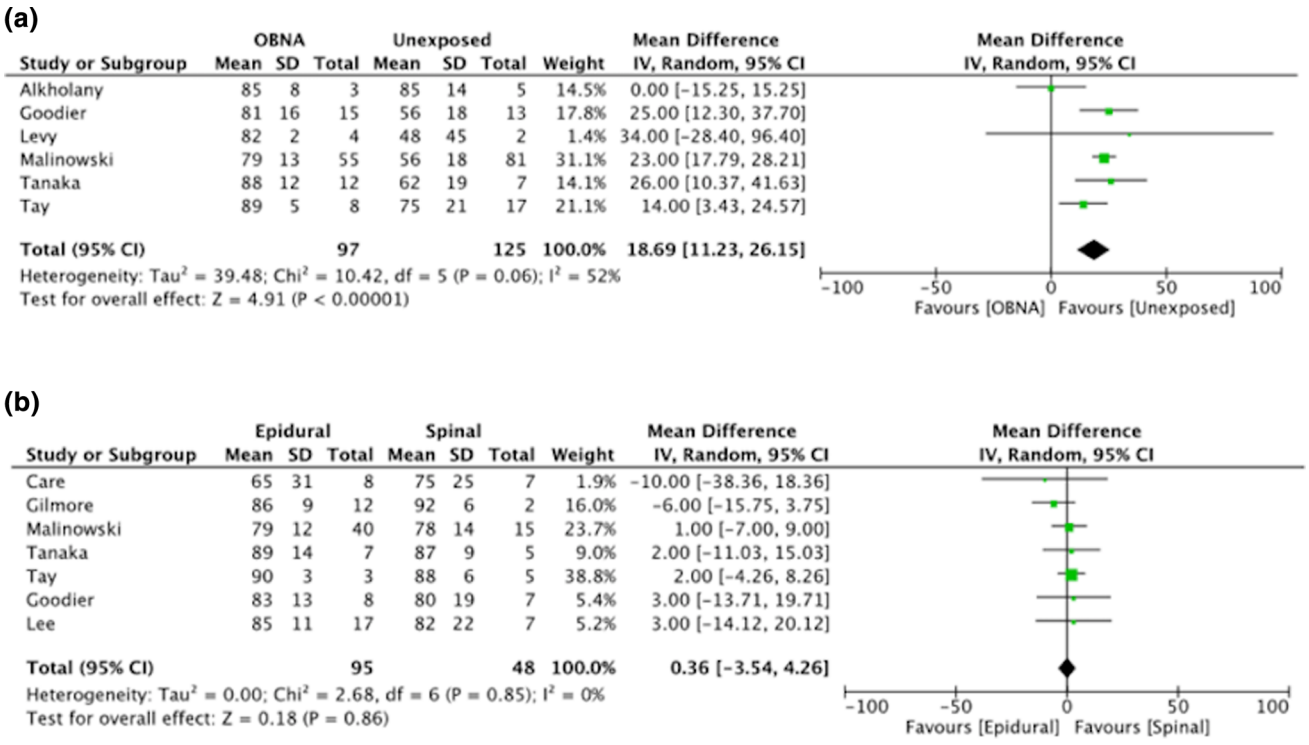

Fig. 3 Meta-analysis of mean differences in platelet counts for (a) pregnancies that received obstetric neuraxial anesthesia (OBNA) compared with pregnancies that did not; and (b) pregnant women who received OBNA in the form of an epidural compared with spinal

in obstetric compared with general perioperative populations,[58] potentially owing to the pregnancy-induced physiologic changes within the coagulation cascade, resulting in a hypercoagulable state.[59]

Yet, although there is no direct evidence of a higher neuraxial hematoma risk in ITP populations relative to the general population, OBNA placement at platelet counts below 80 $\times$ $10^9 \cdot L^{-1}$ (n = 60/160, 38%) continues to remain infrequent in ITP patients. More typically, the reported cases of OBNA placement at severely thrombocytopenic ranges have occurred in individuals in whom the platelet count was unknown at the time of anesthetic placement.[30,38,47,50]

A recent Cochrane review in a non-pregnant population with thrombocytopenia of varying etiology, showed that there is little to no quality evidence to direct anesthesiologists regarding the threshold for safe provision of epidural anesthesia or lumbar puncture.[60] Even less data are available from pregnant patients, thus most guidelines on the management of OBNA in ITP parturients stems from expert opinion or small case series, and the recommendations vary. Some guidelines conservatively recommend a platelet count of 75–80 x $10^9 \cdot L^{-1}$ as the lower threshold for OBNA placement,[61-63] though the rationale for 75–80 x $10^9 \cdot L^{-1}$ as the "safe" lower threshold for regional anesthesia remains unclear, as few studies have correlated platelet counts with laboratory evaluation of primary hemostasis.[39]

Other guidelines and authors do suggest that considering neuraxial anesthesia at platelet counts above 50 x $10^9 \cdot L^{-1}$ for patients with stable counts and no history of bleeding or coagulopathy is reasonable.[39,64] Similarly, the most recent statement form the American College of Obstetricians and Gynecologists suggest acceptability of neuraxial anesthesia at platelet counts $>$ 70 x $10^9 \cdot L^{-1}$, with individualized decisions at platelet counts $<$ 70 x $10^9 \cdot L^{-1}$,[65] while the updated report by the American Society of Anesthesiologists task force on obstetric anesthesia does not include a platelet threshold, and recommends an individualized approach to determination of risk.[7]

The paucity of data with respect to OBNA placement means that an anesthesiologist's clinical judgement on what constitutes a safe platelet count for OBNA is largely modulated by the culture and established practices of the centre in which they work. For instance, a survey of German obstetrical anesthesiologists found that the majority of respondents would not perform OBNA when the platelet count is below 65 x $10^9 \cdot L^{-1}$.[66] Interestingly, the technique was viewed as contraindicated by more anesthesiologists in small centres compared with large ones (72% *vs* 63%), and use of epidural anesthesia varied significantly based on geographic location. Yet variation in the comfort level of providing OBNA at lower platelet counts in ITP exists even in large tertiary centres.[17]

Meanwhile, the uncertainty with respect to the safe lower platelet count threshold for OBNA placement at thrombocytopenic ranges in ITP understandably remains perpetuated by adherence to conservative guidelines of 75–80 x $10^9 \cdot L^{-1}$, which are themselves based on limited data points, thereby creating a cycle that precludes further accumulation of data imperative to prove that placement of OBNA at lower platelet counts in the context of ITP is indeed safe. Alongside some guidelines,[64,67] multiple researchers have also called for a cut-off of 50 $\times$ $10^9 \cdot L^{-1}$ for OBNA placement in the ITP population.[39,68,69]

Others astutely point out that the risk of neuraxial hematoma, although frightening, is small and must be weighed against the risks incurred by general anesthesia, particularly when it is required urgently.[18] Specifically, while the risk of neuraxial hematoma following epidural placement in the general obstetric setting has been estimated at 1:168,000,[13] none of which involved a parturient with ITP, marked morbidity attributed to general anesthesia among thrombocytopenic women who underwent Cesarean deliveries in labour under general anesthesia was reported at 6.5%.[18] In considering the morbidity of obstetric general anesthesia further, it is worth noting that the higher incidence of difficult airways at risk of failed intubation are 1:224–1:390.[70-72] In addition, delayed gastric emptying in pregnancy[37] increases the risk of aspiration.[6] Furthermore, mortality risks have been estimated at 6.5 per million in obstetric patients receiving general anesthesia.[73] Also worth considering is the fact that the risks of morbidities, such as aspiration pneumonia or prolonged intubation, are apt to increase with mounting rates of obesity and other chronic co-morbidities in the obstetric population.[18,74,75] Thus, when considering provision of obstetric anesthesia, in addition to the platelet count, an individualized risk assessment should include the etiology of thrombocytopenia, stability of the platelet count, bleeding history, co-morbid conditions, evaluation of body mass index and airway assessment, likelihood of an urgent Cesarean delivery, and the level of the healthcare provider experience.

Study strengths and limitations

Our study represents the first systematic review published to date on obstetrical anesthetic management and complications in the context of ITP. Its strengths include

the strict inclusion criteria and comprehensive nature of the literature search, incorporating publications from all continents. Integration of individual patient data from nine studies included in the systematic review further strengthens the analysis and adds much-needed data on the subject. The review remains limited by the small numbers of OBNA cases reported worldwide in individuals with ITP, typically in the form of case reports, small case series, and small prospective studies. Indeed, there are no randomized-controlled trials published on this subject. Although overall the risk of bias was fair to moderate, by virtue of study type, the included studies represent a lower tier within the hierarchy of evidence. Despite our study strengths, given its relatively small sample size and the rarity of neuraxial hematoma, particularly in the obstetric population, we cannot conclusively determine the safety of OBNA in ITP patients with platelet counts $< 80 \times 10^9 \cdot L^{-1}$ from these data alone.

Several researchers publishing on the topic have concluded their investigations with a recommendation for larger studies.[17,20,76] Others have called for national registries of procedures performed in thrombocytopenic patients.[18,30] Indeed, these are commendable proposals, though from a pragmatic standpoint the feasibility of such prospective endeavours, large enough to provide a conclusive answer, must realistically be addressed. According to Beilin's calculations, if the risk of neuraxial hematoma in individuals with platelet counts above 100 x $10^9 \cdot L^{-1}$ is assumed to be 1:10,000, then detection of twice that incidence in patients with platelet counts below 100 x $10^9 \cdot L^{-1}$ would require in excess of 200,000 patients.[33] Given the rarity of this condition, with even fewer individuals having progressively lower platelet counts, this undertaking is not likely to be achievable, and certainly not for many decades to come. Hence, in the meantime, every patient should be afforded an individualized discussion of risk and benefit relative to other analgesic measures and wider support for neuraxial anesthesia at lower platelet count thresholds should be considered in this population.

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Author contributions *Liane J. Bailey* was involved in the independent review of all studies, data collection, data interpretation, drafting of the manuscript, and critical revision of the manuscript for intellectual content. *Nadine Shehata* was involved in development of the study concept and protocol, data interpretation, drafting of the manuscript, and critical revision of the manuscript for intellectual content. *Bryon De France* was involved in development of the study concept and protocol, data interpretation, and critical revision of the manuscript for intellectual content. *Jose C. A. Carvalho* was involved in data interpretation, and critical revision of the manuscript for intellectual content. *Ann Kinga Malinowski* was involved in development of the study concept and protocol, independent review of all studies, data collection, data interpretation, drafting of the manuscript, and critical revision of manuscript for intellectual content.

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Appendix: Final MEDLINE search strategy

ITP.ti,ab,kf. or Purpura, Thrombocytopenic, Idiopathic/ or (immune adj3 thrombo*).ti,ab,kf. or (idiopathic adj3 thrombo*).ti,ab,kf. or (autoimmune adj3 thrombo*).ti,ab,kf. or werlhof* disease.ti,ab,kf. or Platelet Count/ or platelet count.ti,ab,kf. or Purpura, Thrombocytopenic/ or Thrombocytopenia/ or thrombocytopeni*.ti,ab,kf.

AND

Anesthesia, Epidural/ or Anesthesia, Spinal/ or Anesthesia, Obstetrical/ or Analgesia, Obstetrical/ or Analgesia, Epidural/ or anesthesia, conduction/ or anesthesia, caudal/ or anesthesia, local/ or ((obstetric* or labo?r or neuraxial* or regional* or spinal* or conduction* or local*) adj5 (anesthesia or analgesia or block* or anesthetic*)).ti,ab,kf. or epidural*.ti,ab,kf. or nerve block/ or autonomic nerve block/ or sphenopalatine ganglion block/ or brachial plexus block/ or cervical plexus block/ or Anesthetics, Local/

AND

exp Pregnancy/ or exp abortion, induced/ or exp delivery, obstetric/ or exp Pregnancy Complications/ or parturient*.ti,ab,kf. or pregnan*.ti,ab,kf. or (labo?r or labo?rs or labo?uring or puerper* or C?esar*).ti,ab,kf. or

Pregnant Women/ or ((forcep* or vacuum or ventouse or instrument* or vaginal or natural) adj3 deliver*).ti,ab,kf.

Summary of results

All databases were searched on May 14, 2018

MEDLINE	1946 to May 14, 2018	206
Embase	1947 to May 11, 2018	490
Web of Science	1900 to May 14, 2018	127
Scopus	To May 14, 2018	54
Cochrane	To April 2018	
Database of Systematic Reviews & Central Register of Controlled Trails	April 2005 to May 9, 2018	17
PubMed in process and publications ahead of print	To May 14, 2018	59
TOTAL		953

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