Diagnostic, preventive and therapeutic evidence in obstetrics for the implementation of patient blood management: a systematic review protocol

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ABSTRACT

Introduction Patient blood management (PBM) is defined as the application of evidence-based diagnostic, preventive and therapeutic approaches designed to maintain haemoglobin concentration, optimise haemostasis and minimise blood loss in an effort to improve patient outcome. We propose a protocol for the assessment of the evidence of diagnostic, preventive and therapeutic approaches for the management of relevant outcomes in obstetrics with the aim to create a framework for PBM implementation.

Methods and analysis Diagnostic, preventive and therapeutic tools will be considered in the gynaecological conditions and obstetrics setting (antenatal care, peripartum care and maternity care). For each condition, (1) clinical questions based on prioritised outcomes will be developed; (2) evidence will be retrieved systematically from electronic medical literature (MEDLINE, EMBASE, the Cochrane Library, Web of Science, and CINAHL); (3) quality of the reviews will be assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist; quality of primary intervention studies will be assessed using the risk of bias tool (Cochrane method); quality of diagnostic primary studies will be assessed using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies); (4) the Grading of Recommendations Assessment, Development and Evaluation method will be applied to rate the quality of the evidence and to develop recommendations.

Ethics and dissemination For each diagnostic, preventive or therapeutic intervention evaluated, a manuscript comprising the evidence retrieved and the recommendation produced will be provided and published in peer-reviewed journals. Ethical approval is not required.

INTRODUCTION

Patient blood management (PBM) is defined as the application of evidence-based diagnostic, preventive and therapeutic approaches designed to maintain haemoglobin concentration, optimise haemostasis and minimise blood loss in an effort to improve patient outcome.1-4 The PBM approach is based on three pillars: (1) optimise erythropoiesis; (b) minimise blood loss and bleeding; and (c) optimise the physiological reserve of anaemia.5 To reach this aim, clinicians involved in the management of patients that require the administration of blood components need to highlight the concept that blood components are unique resources that should be used appropriately, should not be wasted and their administration should be performed within a multidisciplinary, multimodal (eg, the application of a blood
conservation programme that incorporates the aggressive management of preoperative anaemia and tolerance of perioperative anaemia as an important component1) and individualised strategy context.1–4

National and international guidelines have promoted and endorsed the application of PBM especially in the perioperative setting.5–10 For example, perioperative anaemia and the need for allogeneic blood transfusions are associated with negative outcomes after major joint replacement.11 12 The introduction of active blood management programmes, including measures to detect and treat anaemia several weeks before elective primary hip or knee replacement, generated significant improvements in outcomes such as lower allogeneic blood transfusion rates, shorter length of stay and a reduction of readmission rates.1

From pregnancy to the postpartum period including delivery, women may need different types of care in different settings (such as ambulatory during pregnancy, admission in hospital during labour). Indeed, pregnancy is characterised by physiological modifications in circulation, such as an increase in total volume, that is required for placental development and fetal growth. Hence, haemodilution and reduced blood viscosity due to the increase in plasma volume and red cell mass need to be taken into account during blood component management. In addition, compared with the generally transfused population, peripartum women are generally young13 and the long-term consequences such as immunological effects can be critical.14

According to the WHO, causes of maternal mortality can be categorised as direct and indirect. While direct maternal mortality can be the result of complications or management of the pregnancy and delivery (such as pre-eclampsia/eclampsia, haemorrhage, puerperal sepsis, etc), indirect maternal mortality is defined as ‘a pregnancy-related death in a mother with a pre-existing or newly developed health problem unrelated to pregnancy’ (eg, cardiac disease, HIV/AIDS or chronic hypertension). Indirect causes are responsible for about one-fifth of severe maternal outcomes, 50% of which is represented by anaemia.15 Vogel et al found that risk of all perinatal mortality was significantly increased with placental abruption, ruptured uterus, systemic infections/sepsis, pre-eclampsia, eclampsia as well as severe anaemia.16 Postpartum haemorrhage (PPH) is among the leading causes of maternal mortality and morbidity during pregnancy worldwide. Allogeneic blood transfusion is among the most common approaches used in obstetrics to treat PPH and there are sources that warn that rates of transfusion are increasingly being used during childbirth.17 18 Though the majority of deaths occur in low-income countries,19 recent reports indicate that there is an increasing trend in the incidence of PPH over time in Western countries.20 The use of allogeneic blood transfusion should be supported by sound evidence, taking into account the link between transfusion and worsening of clinical outcomes and debated efficacy.21 22 Hence, there is a need to revise the evidence of therapeutic and diagnostic interventions for relevant outcomes in obstetrics and gynaecology in order to produce PBM-based recommendations that are suitable for clinicians and patient decision makers at the local and national level.

The aim of the present protocol is to undertake a literature search of systematic reviews or primary studies regarding therapeutic, preventive and diagnostic interventions necessary to maintain haemoglobin concentration, optimise haemostasis and minimise blood loss in the context of obstetrics and gynaecology. In addition, the present study will provide a framework for adopting PBM through the development of clinical guidelines to assist clinicians, transfusionists, obstetricians and anaesthetists about appropriate care in gynaecology and obstetrics.

METHODS

For each diagnostic, preventive and therapeutic measure, the following steps will be considered:

a. Prioritising critical outcomes and formulating clinical questions;

b. Retrieving the evidence;

c. Developing recommendations.

Prioritising critical outcomes and formulating clinical questions

For each of the potential conditions within the aforementioned phases, the team will prioritise critical outcomes based on the Delphi method. First, a list of relevant outcomes will be submitted to a panel of experts in obstetrics, transfusion medicine, anaesthesiology, clinical epidemiology and public health for evaluation, discussion and ranking.23 24 A maximum of three rounds of consultation will be performed depending on the variability in the ranking of the outcome. In case of large variability in the ranking of the outcomes, the results will be discussed with the panel members before the subsequent round. At the final stage, outcomes will be rated as: critical (score 7–9), important but not critical (score 4–6) or low importance (1–3).

Clinical questions that will take into account the diagnostic tool or the preventive and therapeutic interventions will be formulated based only on critical outcomes.

Setting

The interventions administered to avoid or treat outcomes will depend on the setting, the purpose of the intervention (in terms of prevention or treatment) and the status of the women: (1) antenatal care; (2) peripartum care; and (3) postpartum care within 6 weeks after delivery. The nature of the intervention will depend on the purpose for which it is recommended: (1) prevention or (2) treatment.

In addition, in each condition and setting, the evidence regarding potential diagnostic tools for which a recommendation might be necessary will be proposed.
Retrieving the evidence

For evidence retrieval, we will consider first systematic reviews, and where the evidence is not sufficiently updated or when specific reviews are missing, we will produce new systematic reviews.

Inclusion criteria for systematic reviews

For each condition, to identify the abstracts of interest, we will prepare appropriate search strategies to be run in the following databases (see online supplemental file 1): PubMed, the Cochrane Library and Web of Science.

The following criteria will be considered for SRs (systematic reviews) inclusion: (1) a paper generally defined as a review; (2) any intervention that can be used to prevent or treat critical outcomes in women in gynaecological or obstetrics settings; (3) articles published in English or Italian; and (4) AMSTAR score ≥7. Guidelines will be excluded but will be considered for reference checking to identify potentially relevant SRs.

Pairs of reviewers will independently screen titles, abstracts and full texts. Disagreement will be resolved by discussion and, if necessary, by a third independent reviewer. The process of published study selection will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (figure 1).

The methodological quality of each SR will be assessed using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) instrument. AMSTAR appraises the quality of reviews using the following 11 items: duplicate study selection and data extraction, comprehensive searching of the literature, provision of a list of included and excluded studies, provision of characteristics of included studies, assessment of methodological quality of included studies, appropriate methods for combining results of studies and for assessing publication bias and consideration of conflict of interest statement. Two review authors will independently evaluate the quality of the SRs and disagreement will be resolved by consensus.

Inclusion criteria for primary studies

For the efficacy reviews, we will identify and consider any comparative study, either randomised or non-randomised, that investigated any intervention to prevent and/or treat critical outcomes as appropriate. In general, priority will be given to randomised studies over non-randomised studies.

For diagnostic accuracy reviews, we will consider primarily cross-sectional studies that evaluated the accuracy of tests (such as rotational thromboelastography) to diagnose outcomes of interest within the designated period.

Data extraction and management

Pairs of reviewers will perform data extraction from primary studies independently. Data will be extracted onto study-specific data extraction forms. Information

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**Figure 1** Study screening process.
collected will include trial characteristics (year of publication, country of origin of the study, methodological quality items of the study), patients’ characteristics (number of participants, age, gender), intervention characteristics, comparator characteristics, type of outcome and outcome measures. For diagnostic accuracy studies, the following data will be extracted: clinical features and settings in which the test has been developed, the index test and reference standard or comparator characteristics, description of the target condition.

Assessing the methodological quality of the evidence

For efficacy, evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. For each clinical question, evidence profiles based on the results of the treatment effect will be prepared. The following factors that may affect the rating of quality will be considered: (1) the study design and execution, (2) the consistency of results, (3) the directness of the evidence, (4) the precision of the estimate of the effect and (5) the likelihood of publication bias.

For the risk of bias (study design and execution), we will assess studies according to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential items that can be a source of bias. Review authors will assign each study to one of the following categories: low risk, unclear risk and high risk.

Consequently, the body of evidence will be classified into four categories: (1) high (further research is very unlikely to change our confidence in the estimate of the effect), (2) moderate (further research is likely to have an important impact on our confidence in the effect and may change the estimate), (3) low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) and (4) very low (any estimate of effect is very uncertain).

In case of non-randomised studies, the body of evidence will by default be rated as low but the quality can be upgraded based on the presence of the following three factors: (1) a strong or very strong association, (2) a dose–effect relationship and (3) all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.

For diagnostic evidence, we will use the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) instrument to assess the methodological quality. The QUADAS-2 instrument is made up of four domains: patient selection; index test; reference standard; and flow and timing. Each domain is assessed in terms of risk of bias, with the first three domains also considered in terms of applicability. Pairs of review authors will independently assess the quality that will be rated as ‘yes’, ‘no’ or ‘unclear’.

Assessment of heterogeneity

For efficacy/safety evidence, we will assess heterogeneity according to the approach recommended by the Cochrane Handbook. Where a meta-analysis is possible with at least two studies, we will use the χ² test and I² statistic to assess heterogeneity. We will consider heterogeneity to be statistically significant if the p value is less than 0.1.

For diagnostic accuracy evidence, we will evaluate heterogeneity based on clinical factors, types of interventions, the characteristics of the index test and reference standard.

Data synthesis

For efficacy evidence, we will use risk ratios or ORs along with their 95% CI for binary outcome measures, whereas mean difference with 95% CI will be used to estimate the summary effect for continuous outcome measures and, when data are measured on different scales, the standardised mean difference will be used. We will carry out data synthesis using Review Manager software (V.5). Depending on the expected level of heterogeneity between studies, we will use the random-effects model.

For diagnostic evidence, we will generate a 2×2 table of true positive cases, false positive cases, false negative cases and true negative cases. We will calculate sensitivities and specificities with 95% CIs for each study. We will perform meta-analyses by using the bivariate model. We will use STATA V.13 to generate parameter estimates (logit and variances) and will generate (1) the summary receiver operating characteristic curve, (2) the summary operating point, (ie, summary values for sensitivity and specificity), (3) a 95% confidence region around the summary operating point and (4) a 95% prediction region.

Developing recommendations

The team will discuss and evaluate the net health benefit based on the anticipated balance of benefits and harms across all critical outcomes. For each clinical question, a Summary of Findings (SoF) table will be produced taking into account the gathered evidence. The SoF will summarise the quality of the evidence, the certainty about the balance of benefits versus harms, the similarity in patients’ values and preferences and the costs of an intervention compared with the available alternatives.

The strength of a recommendation will be categorised as ‘strong’ or ‘weak’. It will be determined by the following factors: the quality of evidence, the balance between desirable effects and undesirable ones, the values and preferences and the resources and costs. The strength of a recommendation will be considered strong when the team is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. High or moderate quality of evidence supports strong recommendations when this is also supported by other considerations such as the baseline risk of the population of interest, availability of the service and accessibility to care and costs.
The strength of recommendation will be considered weak when the balance of benefit and harm is uncertain (quality of evidence is low or very low), or when values and preferences are uncertain or when much higher costs are envisaged.30 39

**Patient and public involvement**

Patients and the public were not directly involved in the preparation of the present protocol.

**DISCUSSION**

‘Blood transfusion’ is generally considered as the administration of packed red cells or whole blood,40 platelets,41 fresh-frozen plasma42 or coagulation factors. In particular, allogenic blood transfusion has gained a central role in the management of a wide spectrum of medical and surgical diseases. However, recent progress in the identification and implementation of best transfusion practices on the basis of evidence-based systematic reviews suggests that, compared with a liberal allogenic blood transfusion policy, there was no evidence of negative consequences when following a restrictive blood transfusion policy.40

As PBM is being increasingly introduced in routine clinical practice,10 43–45 there is wide expectation that it will shape the practice of transfusion medicine, the modality of prescription, preparation and administration of blood components as well as the relationship between different disciplines.9 PBM brings a paradigm shift in the concept of blood components which should be considered not only an important resource but also a possible risk factor, with increases in costs, a sometimes limited availability: risky, costly, in limited supply, and their use can worsen negative patient outcomes.46 PBM aims to overcome the ‘product-centred’ concept of blood components and to have a ‘patient-centred’ approach which focusses on improving the health and well-being of the patient.46

In this patient-centred approach, it is required to set up a multiprofessional, multidisciplinary team by involving experts in transfusion medicine, anaesthesiologists and, depending on the context of the specialty, surgeons, orthopaedics or gynaecologists. Introducing transfusion practice improvement through the implementation of PBM can be an effective way of promoting high-value care by ameliorating patient outcomes, reducing blood product utilisation and product-related cost savings.47 48

All the key aspects of PBM are applicable also in the gynaecology and obstetrics setting to treat, prevent outcomes that require the management of anaemia, blood loss, optimise haemostasis and establish decision threshold for transfusion.18 A qualitative study that reviewed national and international guidelines for PBM in obstetrics identified important differences in recommendation for transfusion and PBM. The study emphasised that non-obstetrics guidelines were more likely to contain contemporary approaches to transfusion management than the obstetrics guidelines. The reason for variation may lie in the methods of guideline development, literature review and keenness to include evidence from non-obstetrics settings. These features will be taken into consideration to improve the quality of reporting of the present assessment.

One of the strengths of our study protocol is that we propose the use of the GRADE approach to evaluate the evidence retrieved in the electronic literature. GRADE offers a system of rating quality of evidence for systematic reviews and a method for grading the strength of recommendations in guidelines. GRADE allows the development of a wide range of clinical questions, including therapy, diagnosis as well as prevention. This method indicates a transparent way to frame the question after choosing and rating the outcomes that are considered critical for decision making. Once the evidence is retrieved, GRADE provides tools to rate the evidence by taking into account the risk of bias, the consistency of the body of the evidence, the precision of the effect estimate, any potential publication bias and the direct applicability of the body of the evidence to the patient population for which the recommendation is developed.

The GRADE system suggests ways on how to incorporate evidence with considerations of values and preferences before providing recommendations. This approach has been successfully applied in several settings, one in which we have gained sufficient experience24 39 49 to provide a framework to develop PBM recommendations in obstetrics and gynaecology.

As pointed out by Franchin and Muñoz,43 there are a number of initiatives that have been undertaken by the Italian National Blood Centre to promote the adoption of PBM in Italy, including the release of recommendations for the implementation of PBM in elective major orthopaedic surgery in adults.10

In a general context, the present study will be the first to highlight reviews that address these potential interventions and summarise their results for critical outcomes. At a regional level, the present initiative will be the first to contribute to the development of a framework for PBM recommendations in obstetrics.

**Ethics and dissemination**

A formal ethical approval will not be needed because the data used in this systematic review will not consider individual patient data and there will be no concerns about privacy. The results of the overviews of reviews or systematic reviews for each diagnostic, preventive or therapeutic interventions, a manuscript comprising the evidence retrieved and the recommendation produced will be provided and published in peer-reviewed journals and disseminated in conference presentations.

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