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REVIEW ARTICLE

A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women

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ABSTRACT

Background: Pregnancy-related venous thromboembolism (VTE) is one of the leading causes of maternal morbidity and mortality. **Objectives:** To review the epidemiology, and humanistic and economic burden of pregnancy-related VTE. **Search strategy:** Medline, the Cochrane Central Register of Controlled Trials, Econlit, Science Direct, JSTOR, Oxford Journals, and Cambridge Journals were searched for reports published between January 2000 and December 2012. Keywords related to VTE, pregnancy, and epidemiology and the humanistic and economic burdens were combined. **Selection criteria:** Eligible studies evaluated the incidence, mortality, recurrence, complications, quality-of-life, and economic burden of VTE among pregnant women, and had been published in English. **Data collection and analysis:** Background information of the study, participants' characteristics, and study outcomes were collected. Meta-analyses of data were performed. **Main results:** Twenty studies were included, none of which investigated the economic burden. The pooled overall incidence of pregnancy-related VTE was 1.2 per 1000 deliveries. The pooled VTE case fatality rate was 0.68% and the recurrence rate was 4.27%. The pooled risk of major bleeding was 1.05%. Post-thrombotic syndrome seemed to have a negative effect on quality of life. **Conclusions:** Although the incidence of VTE was found to be relatively low during pregnancy and the postpartum period, the clinical burden is high. Further research is required to assess the economic burden of pregnancy-related VTE.

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1. Introduction

The association between pregnancy and venous thromboembolism (VTE) has been investigated for more than four decades [1]. Thromboembolic events during pregnancy or after delivery are reported frequently because these periods are characterized by hypercoagulability [2]. Indeed, hypercoagulation has been found to increase the risk of VTE events for pregnant women by four to five times in comparison with nonpregnant women of the same age [3]. These VTE events manifest as deep vein thrombosis (DVT) in the legs (80% of cases) and pulmonary embolism (PE; 20%) [4].

Despite evidence that pregnancy-related VTE is one of the leading causes of maternal morbidity and death in high-income countries, its clinical burden has not been adequately established [5]. Apart from the apparent serious short-term consequences, there is evidence indicating that pregnancy-related VTE results in long-term complications such as post-thrombotic syndrome (PTS) [6] and poor quality of life (QoL) [7,8].

Besides the humanistic burden, VTE might also generate an economic burden to pregnant women and healthcare systems. The management of thromboembolic events requires substantial resource use that is further intensified in cases of recurrence and related complications such as major bleeding and PTS [8–10]. However, although the economic burden that relates to VTE has been assessed for other populations (e.g. patients with cancer) [11–14], evidence regarding the economic consequences of VTE among pregnant women is sparse. Because the current global economic environment has led to major cost-containment policies in healthcare systems, it is important for healthcare professionals and decision makers to be aware of the imminent cost of this condition. The objective of the present study was to systematically review and report the epidemiology (incidence), and the humanistic (mortality, recurrence, complications, QoL) and economic burdens of VTE among pregnant women.

2. Materials and methods

The method of the present systematic review was based on the guidelines developed by the Centre for Reviews and Dissemination [15]. The review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [16].

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2.1. Search strategy

Seven databases—Medline, the Cochrane Central Register of Controlled Trials, Econlit, ScienceDirect, JSTOR, Oxford Journals, and Cambridge Journals—were searched for reports published between January 2000 and December 2012. Three major categories of keywords, created by a group of experts, were combined: VTE-related keywords (“venous thrombosis,” “thromboembolism,” “deep-vein thrombosis,” “pulmonary embolism,” “post thrombotic syndrome,” “venous stasis syndrome,” and “chronic thromboembolic pulmonary hypertension”), pregnancy-related keywords (“pregnancy,” “postpartum,” and “ante partum”), and keywords related to epidemiology (“prevalence” and “incidence”) or the humanistic/economic burden (“clinical burden,” “mortality,” “morbidity,” “survival,” “readmission,” “recurrence,” “quality of life,” “complication,” “long term outcomes,” “economic burden,” “cost,” “cost analysis,” “cost of illness,” and “pharmacoeconomics”). The Medical Subject Headings database was used for identification of synonyms. The reference lists of all articles selected for inclusion were scanned to identify potential studies not initially detected by the electronic search. Databases of conference abstracts were not searched: it was supposed that they would not present sufficient data to meet inclusion criteria.

2.2. Study selection

A set of inclusion and exclusion criteria was formed (Box 1), on the basis of which two investigators (G.K. and J.R.) independently screened the identified studies and decided whether they were eligible for inclusion. Two investigators were used to ensure the reliability of the decision. These investigators were researchers (epidemiologists/biostatisticians) with experience in study design, data analysis and systematic reviews.

On the basis of the Centre for Reviews and Dissemination guidelines, all identified studies were firstly evaluated on the basis of titles and/or abstracts. Studies deemed to be irrelevant on the basis of the title or abstract, or that failed to meet at least one of the predetermined criteria

Box 1

Inclusion and exclusion criteria.

Inclusion criteria

- Participants: Women during pregnancy or postpartum period
- Outcomes: Health outcomes (i.e. mortality/survival, readmissions/recurrence, bleeding events, quality of life), the incidence/risk of VTE during pregnancy or the postpartum period in women, or the costs of management of pregnancy-related VTE from either the providers', the national health systems', the society's, or payers' perspective
- Languages: Full text in English
- Study types: prospective studies, retrospective studies, case-control studies
- Countries: All countries

Exclusion criteria

- Study types: Animal studies, systematic reviews and meta-analyses, qualitative studies, case studies/reports, letters to the editor, randomized clinical trials evaluating the efficacy/safety of various strategies for VTE prophylaxis or treatment
- Participants: children, adolescents, or adult populations other than women in pregnancy and postpartum period
- Data: None on relevant outcomes of interest
- Information available: Only abstract

Abbreviation: VTE, venous thromboembolism

were excluded. Subsequently, the full-articles of the remaining studies were retrieved for further investigation.

2.3. Data extraction

A data extraction form was developed to collect background information (journal, year of data use, source of funding, type of study, type of outcome, and location of data), participants' baseline characteristics and demographics (sample size and type of prior VTE), and outcomes (distribution of VTE by stage of pregnancy, follow-up duration, incidence of pregnancy-related VTE, mortality of pregnancy-related VTE, recurrence, complications, and QoL). Data were extracted by the two investigators independently. Any discrepancies between the two investigators were solved by asking a third investigator (N.M.) to extract the data from the relevant study followed by a consensus meeting and discussion among the three investigators.

2.4. Methodological quality assessment

Quality assessment of studies was undertaken using the Critical Appraisal Skills Programme Tool for cohort and case-control studies by two investigators (G.K. and J.R.). Investigators were not masked to study identifiers (e.g. author names, institutions, journals).

2.5. Data analysis

A meta-analysis of the overall incidence of VTE, stratified by the type of VTE (i.e. DVT and PE) and by the period (i.e. pregnancy and postpartum), was conducted in R version 3.1.2 (<https://www.r-project.org/>). Similarly, a meta-analysis of VTE and PE case fatality rate, VTE mortality rate, and VTE recurrence rate was conducted. The Cochran Q test and the I^2 statistic were used to assess the heterogeneity among included studies. I^2 greater than 75% was deemed to indicate high heterogeneity among studies and in such case, a random-effects model was used to pool incidence rates. Moreover, sensitivity analysis by removing one study each time was conducted to identify the study that had the greatest influence on the results. Finally, the Egger test was used to evaluate the potential publication bias.

3. Results

3.1. Search results

After removing duplicate citations, the search of the electronic databases identified 680 unique articles for screening. A total of 20 articles examining the epidemiology and humanistic burden of pregnancy-related VTE and no studies investigating the relevant economic burden were identified (Fig. 1).

3.2. Characteristics of the selected studies

Among the 20 studies selected for inclusion in the review, 10 studies provided only incidence data [3,17–25], eight studies provided VTE-related health outcomes data [6–10,26–28], and two studies provided a combination of incidence and health outcomes data [29,30]. Four studies were prospective [9,10,17,18], 10 were retrospective [3,19–22,26–30], and six were case-control studies [6–8,23–25]. The studies covered a wide range of countries in Europe, Asia, and the USA, and were conducted between 1979 and 2010 (Table 1). Substantial variability was observed with respect to the sample size in the selected studies. Specifically, most studies that aimed to estimate the incidence of pregnant-related VTE had a sample size exceeding 30 000 records (either pregnant women or deliveries), whereas the sample sizes of studies that aimed to report health outcomes associated with pregnancy-related VTE were much smaller (Table 1).

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