

# Systematic Review and Meta-Analysis of the Etiology of Menorrhagia in 2,770 adolescent females

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## Research Article

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# Abstract

## Background:

Adolescent menorrhagia, heavy menstrual bleeding, or abnormal uterine bleeding commonly occur in adolescent woman. The differential diagnosis can be challenging. The mnemonic: PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified), is commonly used but it does not stratify as to the likelihood of a disorder. We have sought to develop a probability-based differential diagnosis for Adolescent menorrhagia, heavy menstrual bleeding, or abnormal uterine bleeding

## Methods:

A comprehensive literature search was conducted using PubMed, EMBASE, and SCOPUS databases. Case series describing adolescents from 10 to 21 years of age with menorrhagia, abnormal uterine bleeding (AUB), or heavy menstrual bleeding (HMB) were acceptable if: more than 10 patients were included; editorials, case reports, and secondary sources such as review articles, or book chapters were excluded. No language filter was used, but an English abstract was required. The etiology of menorrhagia, abnormal uterine bleeding, or heavy menstrual bleeding, and the country of origin was extracted from articles that met inclusion criteria. Cumulative rate estimates were determined by Bayesian probability modeling.

## Results:

17 full text articles were reviewed in detail; 2,770 patients were included. The most frequent causes of menorrhagia were Ovarian Uterine Disorders (23.7%; 95% CrdI 22-25.5%), Coagulation Disorders (19.4%; 95% CrdI 17.8 - 21.1%), and Platelet Disorders (6.23%; 95% CrdI 5.27-7.27%) with 45.9% (95% CrdI 43.8 - 47.9%) of the cases of indeterminate origin.

## Conclusions:

The leading causes of menorrhagia in healthy adolescent females were varied. The sub-analysis identified distinct etiologies, suggesting that multiple factors must be considered in the evaluation of menorrhagia. While PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) provides us with a comprehensive picture of the possible causes of menorrhagia in females, this systematic review assigns probabilities to the etiologies of menorrhagia in adolescent females, providing physicians with a more focused and efficient pathway to diagnosis.

## Background

Among female adolescents, menorrhagia or heavy menstrual bleeding, has an estimated prevalence of 37%<sup>1</sup>. Heavy menstrual bleeding, defined as excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or material quality of life, is currently classified according to the PALM-COEIN system<sup>2</sup>: polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction,

endometrial, iatrogenic, and not otherwise classified. This system, although useful, is not probability based, making it difficult for the physician to develop an efficient diagnostic plan.

Adolescent menorrhagia is typically related to anovulation, however, other causes such as an underlying bleeding disorder must be considered when a healthy female experiences heavy menstrual bleeding at menarche or during adolescence. While the frequency of bleeding disorders in the general population is estimated to be 1–2%, bleeding disorders are found in approximately 20% of adolescent girls who present for evaluation for menorrhagia and in 33% of adolescent girls hospitalized for menorrhagia<sup>3</sup>. The purpose of this systematic review was to (1) determine the general categories of menorrhagia across a wide spectrum of patients and; (2) determine the relative prevalence of specific etiologies using a probability based methodology

## Methods

This systematic review followed The Preferred Reporting Items in Systematic Reviews and Meta-analysis (PRISMA) guidelines<sup>4</sup>.

## Literature Search and Inclusion Criteria

A comprehensive literature search was conducted using the PubMed, EMBASE, and SCOPUS databases. The search items “Abnormal uterine bleeding” OR “menorrhagia” OR “heavy menstrual bleeding” AND “adolescents” were input. Editorials, case reports, review articles, book chapters, and studies with less than 10 patients were excluded. English abstracts were required. No date filter was used in the PubMed and EMBASE database searches. In the SCOPUS search engine, publication data was filtered to include only articles published from 2020 onward to search for newer publications and abstracts. The literature search was conducted by two authors on two separate occasions (August 2021, September 2021). The bibliographies from each of the databases were uploaded into the RefWorks program and exact duplicates were excluded. Each abstract was reviewed independently by two authors (EMH, AER) to identify those studies that met inclusion criteria (**Table 1**); conflicts were resolved by a third author (MTD). Throughout the initial search, relevant review articles were identified, and their bibliographies were reviewed also for studies that could qualify for this review. Full-text articles were reviewed using for inclusion and exclusion criteria.

## Data Extraction

Following the final selection of articles, the etiologies of menorrhagia, heavy menstrual bleeding, or abnormal uterine bleeding, and the number of adolescents affected by each different etiology were recorded for each study.

## Data Synthesis

A Bayesian methodology was employed to determine the rate estimates and the associated 95% credible intervals for each disease entity; the beta distribution was used as the conjugate prior to the conditional likelihood distribution for each rate estimate determined from the extracted data<sup>5,6</sup> All calculations were performed in the R environment.

# Results

## Study Search and Selection

Figure 1 demonstrates the results of the systematic review. The database searches provided a total of 75 results (PubMed- 4 articles, EMBASE- 61 articles, Scopus-10 articles). After exact duplicates were removed, abstracts of 65 articles were reviewed. After exclusion of abstracts that did not meet inclusion criteria a total of 31 full-text articles were examined in detail. Fourteen full text articles were excluded: 7 only studied subpopulations of patients (ie PCOS only), 2 were editorials, 2 failed to meet study criteria once the methods section was examined, 1 only studied therapies, 1 included adults in the study who could not be separated from those less than 21 years of age, and 1 article was a secondary review.

A total of 17 articles (published between 1998–2020) met inclusion criteria and were analyzed for this study.

## Study Characteristics

**Table 2** summarizes the data extracted from the 17 studies. A total of 2,770 subjects were identified. The largest study included 24% of the patient sample. The categories of entities causing menorrhagia in patients less than 21 years of age are shown in Table 3.

Almost half of the cases had no identifiable etiology (45.9%, 95% CredI 43.8–47.9). Ovarian Uterine Disorders (23.7%; 95% CredI 22-25.5), Coagulation Disorders (19.4%; 95% CredI 17.8–21.1), and Platelet Disorders (6.23%; 95% CredI 5.27–7.27). 45.9% (95% CredI 43.8–47.9) accounted for most cases with an identified etiology.

Among the ovarian uterine disorders identified, anovulatory bleeding (98.7%, 95% CredI 97.6–99.5) accounted for almost all of the cases (table 3a); endometriosis (0.564%; 95% CredI 0.117–1.35) and polycystic ovary syndrome (0.564%; 95% CredI 0.117–1.35) were encountered rarely. Among coagulopathies, von Willebrand's Disease (88.1, 95% CredI 84.9–90.9) accounted for the vast majority of cases; Factor 8 Deficiency (6.19%; 95% CredI 4.13–8.64) and Clotting Factor Deficiencies (4.13%; 95% CredI 2.47–6.18) occurred less commonly (table 3b). As a group, platelet abnormalities accounted for a small percentage of patients with menorrhagia; Platelet Function Disorders(37.9%; 95% CredI 30–46), Inherited Thrombocytopenia (17.1%; 95% CredI 11.4–23.8) and Platelet Qualitative Disorders(13.6%; 95% CredI 8.43–19.7) were the most common platelet disorders identified (table 3c).

## Discussion

A systematic review of menorrhagia in patients less than 21 years of age yielded 17 full text articles describing 2,770 adolescent females. These patients spanned the age range of 10–21 years old. Although PALM-COEIN<sup>2</sup> is a useful tool to organize the etiologies of menorrhagia, it fails to provide *a priori* probabilities for each entity or to estimate the number of patients with no identifiable etiology. The present study identifies the etiologies of menorrhagia in a combined cohort of more than 2000 patients, assigns relative probabilities to the etiologies of menorrhagia in adolescents and that over 40% of individuals will have no identifiable etiology. Among patients with an identifiable etiology for f menorrhagia, Ovarian Uterine disorders (23.7%; 95% CredI 22-25.5),

Coagulation Disorders (19.4%; 95% CredI 17.8–21.1), and Platelet Disorders (6.23%; 95% CredI 5.27–7.27) were the most common systematic disorders. Within these categories, anovulatory bleeding, von Willibrand's Disease and platelet function disorders were most common. As a systematic review, this article has inherent limitations. The etiologies of menorrhagia listed in the selected articles were taken as they were reported in their respective studies. This resulted in vague etiologies, such as unspecified thrombocytopenia and aggregation secretion defects. Additionally, the availability of diagnostic resources, criteria, and thoroughness of evaluation were not standardized across institutions, resulting in the large number of indeterminate etiologies of menorrhagia. This also raises the issue of diagnostic consistency.

## Conclusions

The present study, a systematic review found the causes of menorrhagia in healthy adolescent females were varied. The sub-analysis identified distinct etiologies, suggesting that multiple factors must be considered in the evaluation of menorrhagia. While PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified) provides us with a comprehensive picture of the possible causes of menorrhagia in females, this systematic review assigns probabilities to the etiologies of menorrhagia in adolescent females, providing physicians with a more focused and efficient pathway to diagnosis.

## Abbreviations

PALM-COEIN polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified

PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analysis

CredI Credible Intervals

## Declarations

Ethics Approval: No ethics approval was required as all data was pre-existing and found in the public domain.

Consent for publication: NA

Availability of Data and Materials: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interest: None

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Authors' contributions:

Hall: Aided in the design, carried out the searches and did data extraction, aided in manuscript preparation.

Ravelo: Aided in the design, carried out the searches and did data extraction, aided in manuscript preparation.

Aronoff: Aided in design, performed the statistical analysis, aided in manuscript preparation.

Del Vecchio: Aided in design, aided in searches and data extraction, aided in manuscript preparation and submitted final manuscript.

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## Tables

Tables 1 to 3 are available in the Supplementary Files section.

## Figures



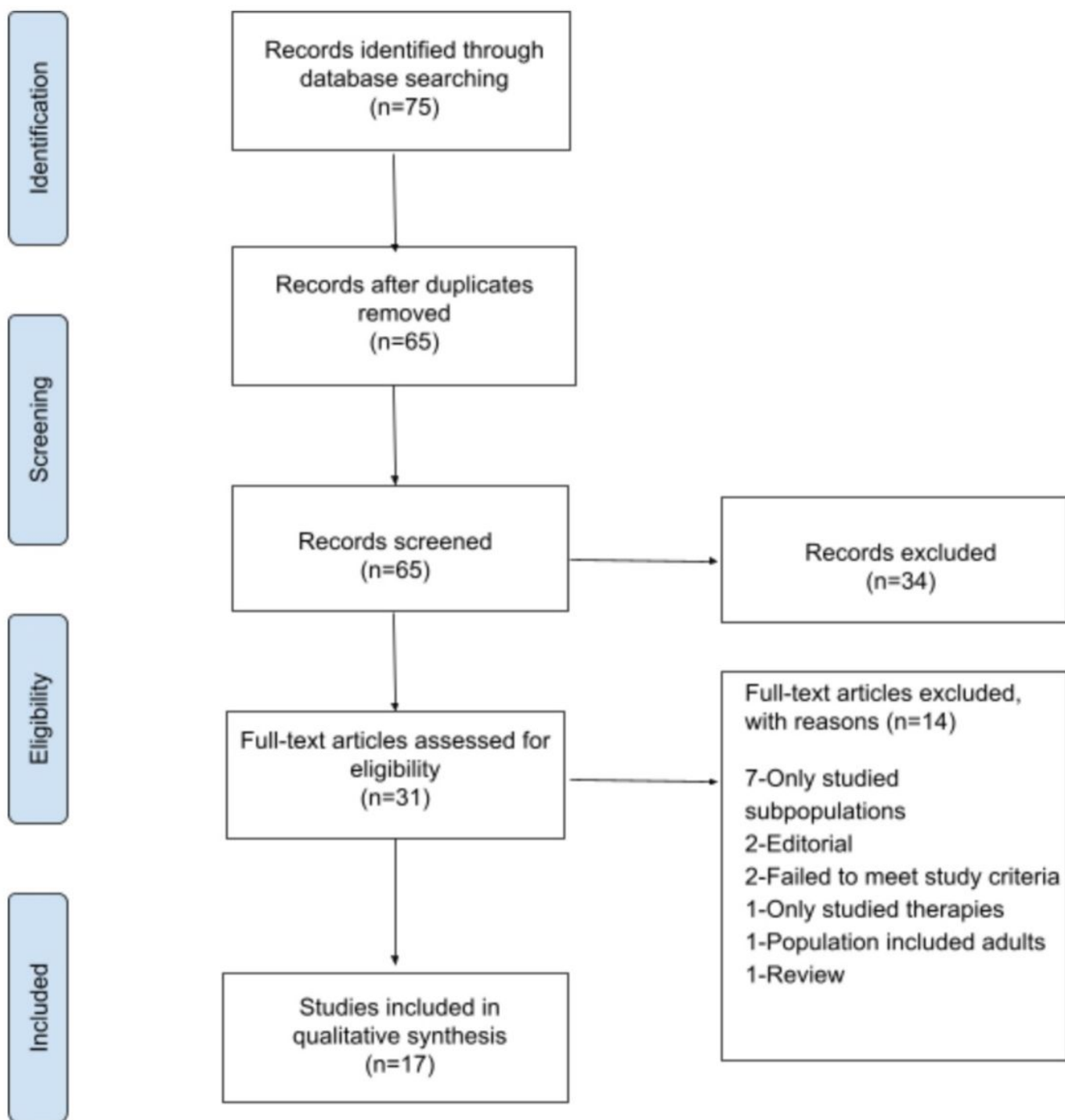


Figure 1

Literature search results. Adapted from Moher et. al. (PLoS Med 2009;6:e1000097)<sup>4</sup>.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.xlsx](#)

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- Table3.xlsx
- Table3A.xlsx
- Table3B.xlsx
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