

The Impact of Dysmenorrhea on Young People's Health-Related Quality of Life

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BACKGROUND

Dysmenorrhea is the most common gynaecological complaint of adolescent girls (Klein & Litt, 1981). It is a condition characterised primarily by recurrent, crampy, lower abdominal pain during menstruation (Sager & Laufer, 2013). Other unpleasant symptoms associated with dysmenorrhea include nausea, vomiting, loss of appetite, headaches, backache, diarrhoea, flushing, sleeplessness, and weakness (Harel, 2006). Dysmenorrhea can be categorised as primary or secondary, with primary dysmenorrhea being the most common type found in adolescents (Klein & Litt, 1981).

Individuals are diagnosed with primary dysmenorrhea when they experience symptoms without any pelvic abnormalities and have a normal ovulatory cycle (Klein & Litt, 1981). The causes of primary dysmenorrhea are not fully understood, although mechanisms such as myometrial hypercontractility (MH) and arterioral vasoconstriction (AV) are thought to contribute to menstrual pain (Akerlund, 1994; Woodbury, Torpin, Child, Watson, & Jarboe, 1947). Factors associated with MH and AV include an excessive secretion of prostaglandins (Tzafettas, 2006), which are initiated in the uterus during menstruation (Alvin & Litt, 1982), and abnormal plasma levels of vasopressin (Åkerlund, 2006; Tzafettas, 2006). Other possible contributors to menstrual pain include oxytocin receptor immunoreactivity, cytokine gene expression profiles of peripheral blood mononuclear cells (Ma et al., 2013; Nie, Liu, & Guo, 2010) and increases in innervation of the endometrial and myometrial layers of the uterus (Aguilar & Mitchell, 2010). Although these factors are associated with dysmenorrhea, more research on uterine contractility is needed (Aguilar & Mitchell, 2010) to fully understand the mechanisms behind menstrual pain.

Secondary dysmenorrhea, seen in approximately 10% of adolescents and young adults with painful menstruation, is associated with pelvic abnormalities (Harel, 2006), the most common of which is endometriosis, i.e., the presence and growth of endometrial glands and stroma outside of the uterine cavity (Harel, 2006). Although endometriosis is often associated with adult women, it is highly prevalent in adolescent girls (aged 10-21) undergoing laparoscopic investigation (62%) and adolescent girls with dysmenorrhea (70%) (Janssen, Rijkers, Hoppenbrouwers, Meuleman, & D'Hooghe, 2013). Dysmenorrhea is primarily a

cyclic pain; however, recurrent nociceptive inputting as a result of painful menstruation can result in neuronal alterations, leading to acyclic chronic pain (Vincent et al., 2011).

To determine the prevalence and possible correlates of menstrual pain, Klein and Litt (1981) conducted a representative survey of 7000 non-institutionalised American adolescents (12-17 years). Of that sample, 2699 were menarchal girls who reported a high prevalence (59.7%) of discomfort or pain associated with menstruation. Of those 59.7% who reported pain, 14% described the pain as severe, 37% as moderate, and 49% as mild. The prevalence of dysmenorrhea increased with age (39% of 12 year olds and 72% in 17 year olds) and sexual maturity (38% in adolescents at tanner stage three and 66% at tanner stage five). More recent studies have reported similarly high prevalence rates of dysmenorrhea (55-85%) among adolescent girls (Banikarim, Chacko, & Kelder, 2000; Strinić et al., 2003). However, in the Klein and Litt study only 29% of those reporting severe pain and 14.5% of the entire sample had sought medical help (Klein & Litt, 1981). It appears that although dysmenorrhea prevalence rates are high, many young girls do not present their symptoms to medical professionals.

In addition to not presenting to medical professionals, many young girls with dysmenorrhea are using often ineffective, non-pharmacological methods to relieve their symptoms (Campbell & McGrath, 1999). In a study of 289 school girls (Campbell & McGrath, 1999), nearly all the sample (98%) used only non-pharmacological methods such as heat, rest or distraction to treat dysmenorrhea despite perceiving the efficacy of these methods as low (40%). However, another study found that 73% of adolescent girls experiencing dysmenorrhea knew of medications that could relieve menstrual pain (Banikarim, Chacko, & Kelder, 2000). The combination of under-reporting and reliance on, often ineffective, non-pharmacological methods suggests that dysmenorrhea is poorly managed in the adolescent population and it is therefore unsurprising that numerous studies investigating the impact of adolescent dysmenorrhea on health-related quality of life (HRQoL) found it to have a profound negative impact on various aspects of life (Banikarim et al., 2000; Chaudhuri & Singh, 2012; Tinatin Gagua, Besarion Tkeshelashvili, David Gagua, & Nino Mchedlishvili, 2013; Klein & Litt, 1981; Nur Azurah, Sanci, Moore, & Grover, 2013).

HRQoL is a multidimensional construct encompassing physical, social, and psychological functioning, and well-being (Colwell, Mathias, Pasta, Henning & Steege, 1998; Hays, Anderson, & Revicki, 1993). HRQoL is measured with generic or disease specific

instruments which include measures of physical, social and psychological functioning, and many measures require patients to both report their current functioning within those domains and also report how they value their current functioning (Levine, 1987) or their satisfaction with that compared to how participants would ideally like to be functioning (Levine, 1987). Wilson and Cleary (1995) proposed a model outlining the process by which an individual's physical health status, such as experiencing dysmenorrhea, impacts on their quality of life (QoL). They posited that biological and physiological variables may lead to physical and psychophysical symptoms, which can then affect functioning and overall HRQoL (Wilson & Cleary, 1995).

Based on this multidimensional definition of HRQoL, studies investigating the impact of dysmenorrhea on adolescent HRQoL have found limitations in all domains of functioning. Klein and Litt (1981) found that 14% of adolescents frequently missed school because of dysmenorrhea. Chaudhuri and Singh (2012) reported high rates of sickness absenteeism (25.8%) among school girls due to menstrual cramps, as well as difficulty concentrating and poor school performance. Recent studies have found adolescents with dysmenorrhea to have lower physical functioning compared to young females with other menstrual problems (Nur Azurah et al., 2013), and significantly higher levels of depression and anxiety compared to healthy controls (Gagua, Tkeshelashvili, Gagua & McHedlishvili, 2013). It should be noted that the data on adolescent dysmenorrhea was collected from a variety of different cultures where attitudes about menstruation and gender differ from one another. Despite this, it appears that dysmenorrhea, with its high prevalence and under-reported, poorly managed symptoms, impacts on every aspect of life of the young females who experience it.

Despite evidence that dysmenorrhea is associated with limitations in HRQoL, existing reviews have primarily focussed on the biomedical aspects of adolescent menstrual pain rather than how the experience of pain and other related symptoms impacts on the lives of adolescent girls. Some reviewers have briefly commented on aspects related to HRQoL, such as a very early study by Ylikorkala and Dawood (1978), who focussed on the aetiology of primary dysmenorrhea in adolescent and adult women. Despite focussing on aetiology, these authors produced a short summary of the impact of primary dysmenorrhea on school and work attendance, concluding that overall, post-menarchal women lost approximately 140 million hours of school and work annually in America. Davis and Westhoff (2001) conducted a mini systematic review examining the prevalence, associated morbidity, and treatment of

primary dysmenorrhea in adolescent girls. This review did briefly address the impact of primary dysmenorrhea based on school and activity participation although other HRQoL aspects were not reviewed. Recently, two review articles have aimed to provide a comprehensive overview of dysmenorrhea and endometriosis in young women (Gagua, Tkeshelashvili, & Gagua, 2012; Harada, 2013). However again, these focussed on biological aspects including aetiology, prevalence, symptoms and management of dysmenorrhea and endometriosis, neglecting the impact that the pain has on the adolescents themselves. Gao et al. (2006) conducted a systematic review of the burden of endometriosis, one of the primary causes of secondary dysmenorrhea, on the HRQoL of adults and adolescents. They found that endometriosis was associated with impaired HRQoL, including pain, psychological functioning and social functioning. In addition to the evidence summarised above, this review shows that gynaecological symptoms such as pain have a profound impact on the lives of adolescents. Despite this, there has not yet been a comprehensive and systematic review of the literature relating to dysmenorrhea (primary and secondary) and its impact on the HRQoL of young girls (<18 years old).

Review Question

The aim of the present systematic review is to investigate, using evidence from the existing literature, what impact primary and secondary dysmenorrhea has on the HRQoL of adolescents (<18 years old). The review objectives are therefore as follows:

1. Examine studies that measure HRQoL, as a main outcome or its constituent parts, in adolescent females (<18 years old) experiencing primary or secondary dysmenorrhea.
2. To identify gaps in the relevant literature on the impact of dysmenorrhea on HRQoL and make recommendations for future research.

METHOD

Criteria for Study Inclusion

Types of Study:

Observational studies, including cohort, cross-sectional and case control investigations will be included. The following types of study will be excluded from this review: randomised control trials (RCTs)..

Types of Participant:

Studies will be included if they investigated the impact of self-reported dysmenorrhea on the HRQoL in a) post-menarchal, b) female, c) adolescents <18 years old, d) experiencing either primary or secondary dysmenorrhea e) of any severity. Studies that include both adult and adolescent data, will be excluded except in cases where adolescent data (<18years) has been provided separately

Outcomes of Interest:

A broad definition of HRQoL will be adopted, which will include the following domains: Physical, social, and psychological functioning and well-being (Hays et al., 1993). Reports of actual functioning compared to how participants would ideally like to function will be reviewed as an indication of well-being (Ryan & Deci, 2001). Studies that measure any constituent aspects of HRQoL will be included. Studies that have used a wide range of measures will be accepted, including generic multidimensional (used to measure health status of any medical condition) and condition-specific HRQoL instruments.

As a result of an initial scoping of the literature, aspects of HRQoL of particular interest include: physical functioning, school functioning, emotional functioning (such as depression and anxiety) and social functioning.

Piloting the Inclusion Criteria

Before conducting the systematic review, the primary researcher will evaluate how appropriate the provisional inclusion criteria are by using them to decide whether a small selection of sample papers will be included in the review (Akers, 2009).

Search Strategy

A thorough search will be conducted to identify all relevant studies. Each step will be documented to allow for peer review and replication. Searches usually retrieve a large number of titles and abstracts that do not meet the inclusion criteria; however, by reducing sensitivity of the search, it is possible to miss relevant and important studies (Higgins & Green, 2008). This search will therefore aim to identify all relevant published papers from the following databases: CINAHL (1960- present), MEDLINE (1960-present), EMBASE (1974-present) and PsychINFO (1960-present).

The search will be conducted in two stages. In the first stage, pre-determined search terms will be run through the electronic databases stated above. The pre-determined search terms were generated by the research team following an initial scope of the literature relevant to adolescent dysmenorrhea and HRQoL. Initial scoping also informed the date to which searches were set, with the exception of the EMBASE (via ovid) database which was pre-set. Following this, a secondary search of the databases will be conducted using key words identified from articles retrieved by the initial search.

Other methods of searching will include: Visual inspection of the reference lists of key studies, hand searching key journals (including 'Journal of Pediatric and Adolescent Gynaecology'), contacting relevant authors, searching relevant internet sources (Google Scholar), BIOSIS previews, and citation searches using PsychINFO and Google Scholar.

Pre-determined Search Terms

Search: CINAHL (via EBSCO), filtered by English Language and Date (1960-2014)

S1: "Adolescen*"

S2: "Child"

S3: "paediatric*"

S4: "pediatric*"

S5: "young females"

S6: "school girls"

S7: S1 OR S2 OR S3 OR S4 OR S5 OR S6

S8: "dysmenorrh*"

S9: "Endometriosis"

S10: "menst* disorders"

S11: "pelvic pain"

S12: "chronic pelvic pain"

S13: "menstrual cycle"

S14: “period pain”

S15: “painful mens*”

S16: S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

S17: “Quality of Life”

S18: “health-related quality of life”

S19: “QoL”

S20: “HRQoL”

S21: “well-being”

S22: “Family Function*”

S23: “school function*”

S24: “school absen*”

S26: “school attendance”

S27: “academic performance”

S28: “social isolation”

S29: “social function*”

S30: “emotional function*”

S31: “physical function*”

S32: “psychological function*”

S33: “depress*”

S34: “anxiety”

S35: “affect”

S36: “mood”

S37: “disab*”

S38: “peer relationships”

S39: S17 OR S18 OR S19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28
OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 O5 36 OR 37 OR 38

S39: S7 AND S16 AND S39

Search: MEDLINE (via EBSCO) filtered by English language and date (1960-2014)

S1: “child”

S2: “adolescen*”

S3: “paediatric*”

S4: “pediatric*”

S5: “young females”

S6: “school girls”

S7: S1 OR S2 OR S3 OR S4 OR S5 OR S6

S8: “dysmenorrh*”

S9: “endometriosis”

S10: “menst* disorders”

S11: “pelvic pain”

S12: “chronic pelvic pain”

S13: “menstrual cycle”

S14: “period pain”

S15: S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14

S16: “quality of life”

S17: “health-related quality of life”

S18: “QoL

S19: “HRQoL”

S20: “well-being”

S21: “family function*”

S22: “school function*”

S23: “school absen*”

S24: “school attendance”

S25: “academic performance”

S26: “social isolation”

S27: “social function*”

S28: “emotional function*”

S29: “physical function*”

S30: “psychological function*”

S31: “depress*”

S32: “anxiety”

S33: “affect”

S34: “mood”

S35: “disab*”

S36: “peer relationships”

S37: S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR
S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36

S38: S7 AND S15 AND S37

Search: EMBASE (via ovid) filtered by English language and Date (1974, as set by the
database-2014).

1. Adolescen*.mp.
2. Child.mp.
3. Paediatric*.mp.
4. Paediatric*.mp.
5. (young adj females).ti,ab.
6. (school adj girls).ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Dysmenorrh*.mp.
9. Endometriosis.mp.
10. (menst* adj disorders).ti,ab.
11. (pelvic adj pain).ti,ab.
12. (chronic adj pelvic adj pain).ti,ab.
13. (menstrual adj cycle).ti,ab.
14. (Period adj pain).ti,ab.
15. (painful adj mens*).ti,ab.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. (quality adj of adj life).ti, ab.
18. (health adj related adj quality adj of adj life).ti, ab
19. QoL.mp.
20. HRQoL.mp.
21. (well adj being).ti,ab.
22. (family adj function*).ti,ab
23. (academic adj achievement).ti,ab
24. (school adj function).ti,ab
25. Absenteeism.mp.
26. (school adj absen*).ti,ab
27. (school adj attendance).ti,ab
28. (academic adj performance).ti,ab
29. (social adj isolation).ti,ab
30. (social adj function*).ti,ab
31. (emotional adj function*).ti,ab
32. (physical adj function*).ti, ab
33. (psychological adj function*).ti,ab

- 34. Depress*.mp.
- 35. Anxiety.mp.
- 36. Mood.mp.
- 37. Affect.mp.
- 38. Disab*.mp.
- 39. (peer adj relationships).ti,ab
- 40. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
- 41. 7 and 16 and 40

Search: PsychINFO (via EBSCO) filtered by English language and date (1960-2014)

S1: adolescen*

S2: child

S3: paediatric*

S4: pediatric*

S5: "young females"

S6: "school girls"

S7: S1 OR S2 OR S3 OR S4 OR S5 OR S6

S8: dysmenorrh*

S9: endometriosis

S10: "menst* disorders"

S11: "pelvic pain"

S12: "chronic pelvic pain"

S13: "menstrual cycle"

S14: "period pain"

S15: "painful menst*"

S16: S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

S17: “quality of life”

S18: “health-related quality of life”

S19: QoL

S20: HRQoL

S21: “well-being”

S22: “family function*”

S23: “school function*”

S24: “school absen*”

S25: “school attendance”

S26: “academic achievement”

S27: “social isolation”

S28: “emotional function*”

S29: “social function”

S30: “physical function”

S31: “psychological function”

S32: depress*

S33: “anxiety”

S34: mood

S35: affect

S36: disab*

S37: “peer relationships”

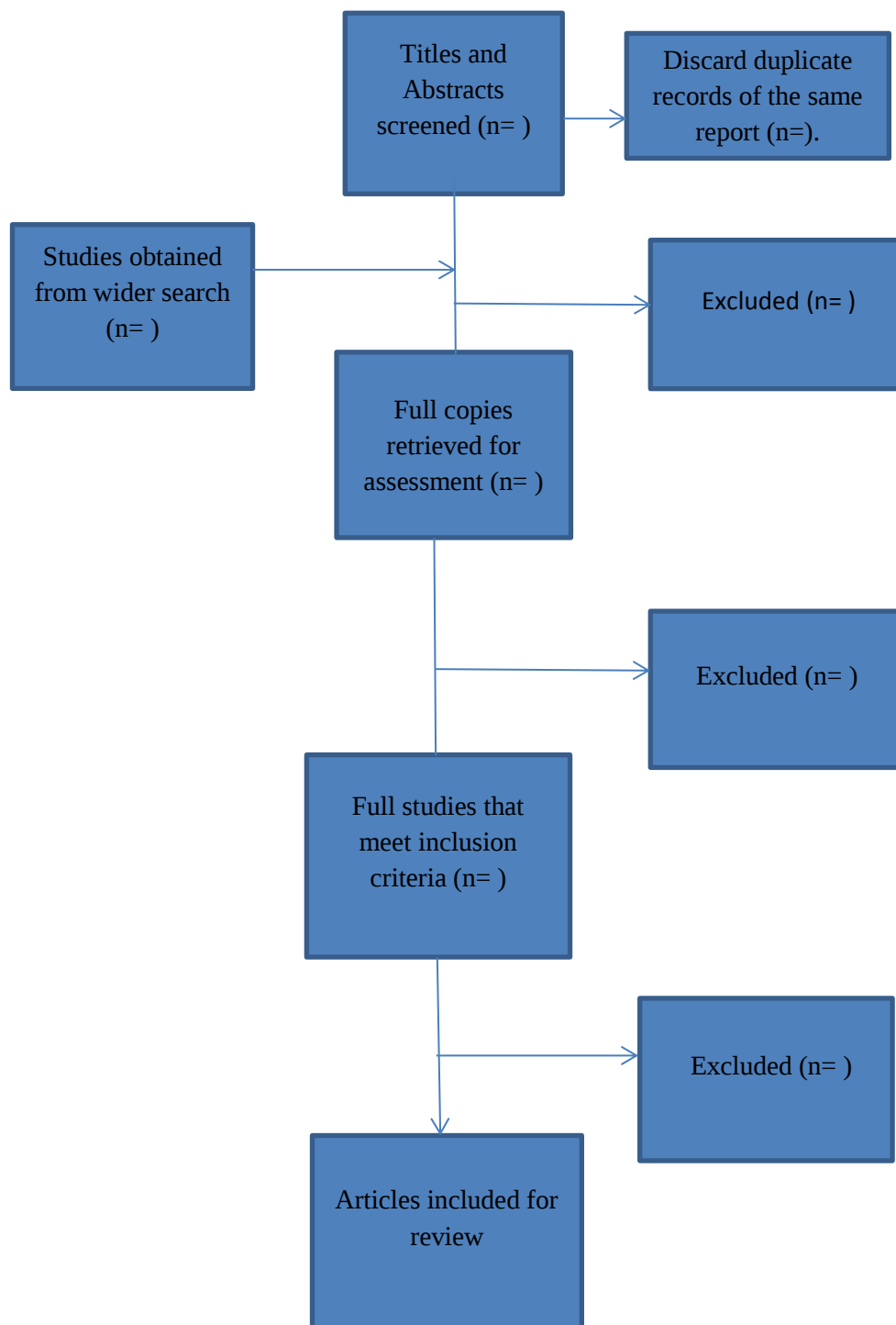
S38: S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR
S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37

S39: S7 AND S16 AND S38

Search Flow

The primary researcher (PHJ) will carry out the process of study selection (Fig.1) which will consist of two stages (Akers, 2009). During the first stage, all abstracts and titles generated from the initial search will be screened. Decisions regarding the inclusion/ exclusion of titles will be documented and verified by academic supervisors pending discussion. The second stage will consist of screening the full papers identified as potentially relevant in the initial screening stage.

Figure 1: Search strategy flow chart (Moher, Liberati, Tetzlaff, & Altman, 2009)



Updating Literature Searches

The primary researcher will conduct an update of the literature searches towards the end of the project to ensure that no recent papers have been missed in the review.

Managing References

The primary researcher will be responsible for ordering inter-library loans and recording the receipt of documents. EndNote will be used to record and manage references, identify and remove duplicate references, and document the literature searching process while allowing all members of the research team shared access to the reference library. The primary researcher will be responsible for adding and deleting references to the library, and informing other members of the research team of these actions.

Data Extraction from included studies

Data extraction needs to be as reliable and un-biased as possible (Akers, 2009). Therefore, a tabulated guide to the data extraction process has been developed. For each included study, the following information will be obtained:

Table 1.1: General study information

Study number	
Date of data extraction	
Author	
Title	
Citation	
Type of publication	
Country of origin	
Source of funding	

Table 1.2: Study characteristics

Aim	
Design	

Table 1.3: Participant demographic and medical characteristics

Number of	
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participants	
Inclusion criteria	
Exclusion criteria	
Recruitment procedures used	
Age	
Ethnicity	
Socio-economic status	
Menstrual characteristics	
Dysmenorrhea characteristics	
Co-morbidities	

Table 1.4: Measures and analysis used

What was reported	
Definition used	
Measurement tool	
Unit of measurement	
Type of analysis	

Table1.5: Outcomes/ results

	Dysmenorrhea Group	Control Group (if applicable)
Withdrawals from study?		
Outcomes/ results of analysis		

To maximise accuracy the primary researcher will go through each of the included studies and fill out the data extraction forms and then another researcher (CL) will check that the forms have been filled out correctly and in as much detail as possible.

Quality Assessment Tool

The use of a quality assessment tool in assessing observational studies is not as well established as those that assess the quality of randomised controlled trials, leading many researchers to abandon the use of a checklist or develop their own (Mallen, Peat, & Croft, 2006). Checklists are a reliable means of ensuring that all the included studies are assessed in a standardised way (Akers, 2009). Therefore, a modified version (appendix A) of the Downs and Black checklist for non-randomised studies will be used to assess the methodological quality of the included studies (Downs & Black, 1998). Questions will be modified by the research team, based on Akers (2009)'s guidelines regarding risk of bias in observational studies. Each study will receive a score for quality in three areas: reporting, external validity bias, and selection bias and power (appendix A). Higher scores indicate better quality in each category.

Because some items included in the checklist may require a degree of subjective judgement, the checklist will be piloted and quality assessment will be conducted by two researchers (PHJ, CL) independently. All quality assessment information will be reported individually in summary tables and then incorporated into the narrative synthesis where differences in methodological quality will be discussed in terms of study results.

Data Synthesis

Descriptive Summary

The results section will begin with a clear, descriptive summary of all the studies and include summary tables that will briefly outline each individual study:

Table 2.1: Descriptive summary table of included studies

<u>Study</u>	<u>Aims/ Objectives</u>	<u>Study Design</u>	<u>Participant Characteristics</u>	<u>Measures Used</u>	<u>Results</u>

Table 2.2: Quality assessment scores

<u>Study</u>	<u>Overall Risk of Bias Index</u>	<u>Quality of Reporting</u>	<u>External Validity and Bias</u>	<u>Selection Bias and Power</u>

Narrative Synthesis

Popay et al.'s (2006) framework for conducting a narrative synthesis, consisting of four stages, will be followed. In the first stage, theory development, the primary researcher will synthesise theories of how and why adolescent dysmenorrhea may impact adolescent HRQoL.

In the second stage, the researcher will develop a preliminary synthesis of the included studies which will begin with collating, organising, and describing all of the findings. This will include descriptions of the direction and size of effect of dysmenorrhea on all reported aspects of HRQoL, and then grouping the included studies, looking for patterns across and within them. The findings of each study will be tabulated so that the HRQoL outcomes for each study can be viewed more easily, and preliminary assessments of impact of adolescent dysmenorrhea of HRQoL can be assessed.

In the third stage, relationships within and between all of the studies will be explored, patterns emerging from the data during the previous stage will be identified, and critical analysis used to identify factors that might explain variations in study outcomes.

Finally, in the last stage of the synthesis, the robustness, in terms of methodological quality and analysis processes, of the narrative synthesis will be assessed. The credibility of the synthesis will depend on both the quality and quantity of the evidence analysed and the method of synthesis and transparency of its description (Akers, 2009). Weighting will be given to the included studies in terms of methodological quality, potential sources of bias will be discussed, and reasons for different weightings will be justified in the synthesis. Discussion will follow regarding the method of synthesis used, the quality of the included

studies, and the potential influence of both these factors on the overall systematic review results.

Discussion

The purpose of the discussion section of the report will be to help the reader interpret the results of the review, outline strengths and weaknesses of the review, place the findings in the context of the existing evidence base and relevant reviews, and explore the implications of the findings in terms of clinical practice and further research.

Dissemination

It is hoped that the findings of this systematic review will contribute to increased knowledge among young girls and their parents in relation to adolescent dysmenorrhea and that this may help improve the quality of health care and HRQoL. Any conclusions made need to be effectively communicated to the target population for dissemination, including general practitioners (GPs), paediatric gynaecologists, researchers, and young girls and their parents. These results will be submitted for publication to academic journals, presented at conferences, and written up for inclusion in condition related web sites.

Registering and Reviewing the Protocol

Previous versions of the protocol were peer reviewed by two paediatric gynaecologists with a special interest in adolescent dysmenorrhea who helped the review team to clarify medical terminology, and two academic psychologists with expertise in systematic reviews who gave feedback on the search terms and search strategy, to which the protocol was modified accordingly. The systematic review methodology will be registered to PROSPERO, an international database of prospectively registered systematic reviews.

Appendix A

All Criteria	Description of Criteria	Possible Answers
1	Is the hypothesis/aim/objective of the study clearly described? Must be explicit.	YES/NO
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered NO. All primary outcomes should be described for YES	YES/NO
3	Are the characteristics of the participants clearly described? -In cohort studies, inclusion and/ or exclusion criteria should be given. -In case-control studies, a case-definition and the source for controls should be given. -In follow-up studies, the characteristics of participants lost to follow-up must be described and losses of participants must be taken into account to score YES.	YES/NO
4	Are the characteristics of dysmenorrhea clearly described? (i.e. severity, duration)	YES/NO
5	Are the distributions of principle confounders in each group of participants to be compared clearly described? A list of principle confounders (e.g. age, severity), has to be provided to score YES.	YES/NO
6	Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions	YES/NO
7	Does the study provide estimates of the random variability in the data for the main outcomes? -In non-normally distributed data the inter-quartile range of results should be reported. -In normally distributed data the standard error, standard deviation or confidence intervals should be reported	YES/NO
8	Have actual probability values been reported (e.g. .035 rather than <.05) for the main outcomes except where the probability value is less than .001? If no significance comparison has been made, score NO	YES/NO
9	Were the young people asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for participants and describe how the participants were selected.	YES/NO
10	Were those people who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.	YES/NO
11	Was the end sample representative of the population from which they were recruited?	YES/NO
12	Was a control group (healthy or with another condition) recruited? If so, were they: -Recruited from the same population (if appropriate)	YES/NO

	-Adequately matched -Recruited over the same time period Case-control studies that fulfil all of the above score YES Cross-sectional and cohort studies score NO.	
13	If any of the results of the study were based on “data dredging”, was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated.	YES/NO/UTD/NO DATA DREDGING
14	Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do score NO	YES/NO/UTD
15	Were the main outcome measures used accurate (for example, valid and reliable)? -Where outcome measures are clearly described, which refer to other work or that demonstrates the outcome measures are accurate score YES. -ALL primary outcomes valid and reliable for YES -If the authors only demonstrate one of validity or reliability and not the other, score NO.	YES/NO/UTD
16	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as NO. If no significant difference between groups shown then YES	YES/NO/UTD
17	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%? Sample sizes have been calculated to detect a difference of x% and y%.	YES/NO/UTD/NOT APPLICABLE

Scoring: Scores will be separated into three categories.

Scores:

YES=1

NO DATA DREDGING=1

NOT APPLICABLE=0

NO=0

UTD=0

Reporting: Scores from questions 1-8

External validity and bias: Scores from questions 9-15

Selection bias and power: Scores from questions 16-17

Overall score=/17

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