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I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla

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Aim and Scope

Our journal is an opened access international journal devoted to peer-reviewed contributions dealing with clinical medicine and medical education from experimental to clinical aspects. Our journal publishes only high quality research, review and other types of original articles, technical and clinical reports every two months. Reviews of various global and Asian aspects will be solicited. Innovation or epidemiological aspects as well as health system research will be addressed. Rigorous systematic review and neglected tropical diseases are our priority

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FORMER

Khon Kaen Medical Journal (KKMJ)

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message from the editor

Hello readers! I hope this message finds you well. We are now in the third issue of this year. One of our original articles is about the time of self-harm and risk for death using the 20-years database of patients visiting the emergency department. Self-harm is not a leading cause of death in Thailand. To ascertain the relationship between time of self-harm and death, one must collect the patients as many as possible, using the 20-year database might be the only possible option to do so. I do hope that our articles help our readers understand more about medicine and to assist your practice in some way.

Thammasorn Jeeeraaumponwat, M.D., Ph.D.
Editor-in-Chief of The Clinical Academia

submission

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For online submission

Our issues of each volume will be published online
on
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reviewing process

All accepted articles are classified into two main categories;
"***standard submission***" with the approximated processing time of 3-4 months and "***expression submission***" with the approximated processing time of 1-2 months. For the latter category, the author must submit as standard submission with notifying our journal for express submission.

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Contents

International Committee of Medical Journal Editors (ICMJE)

Recommendation for Preparing for Submission

1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and STARD for studies of diagnostic accuracy. Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, select¬ing, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network and the NLM's Research Reporting Guidelines and Initiatives.

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.
Author information: Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the Abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of Figures and Tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because Tables and Figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Conflict of Interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not over-interpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a

registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository, authors should state at the end of the abstract the data set name, repository name and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer)." Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your finings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations Related to References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests.Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the

NLM's Citing Medicine, 2nd edition. These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

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Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Diabetes mellitus and risk for Meniere's disease in patient with hearing loss

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To examining the association between diabetes mellitus and the risk for Meniere's disease in patient with hearing loss.

METHODS

We conducted a hospital-based nested case-control study in patients with hearing loss to identify whether diabetes mellitus is the risk for Meniere's disease in the patients with hearing loss. Case patients were those with hearing loss and Meniere's disease while control patients were those with hearing loss alone at Srinagarind Hospital, Thailand. Each case of case patient was matched 1:1 with age and gender to one control patient. Medical records of the eligible case and control patients were reviewed.

RESULTS

There were 287 case patients and 287 control patients were reviewed. It found that diabetes was not associated with Meniere's disease; 10.5% in controls and 9.8% in cases (adjusted odds ratio (AOR), 0.84; 95% CI, 0.46 to 1.52). Moreover, male gender, age, hypertension, and dyslipidemia were not associated with having Meniere's disease. However, higher BMI was associated with having Meniere's disease in patients with hearing loss (AOR, 1.05; 95% CI, 1.01 to 1.09). For the subgroup analysis of case and control patients with diabetes, It found that serum level of HbA1c, age, and diabetic treatment were not significantly associated with having Meniere's disease.

CONCLUSION

The results of this world largest collection of Meniere 's disease suggested that there was no association between diabetes mellitus and risk for Meniere's disease.

INTRODUCTION

Meniere's disease is an aural disorder with a membranous labyrinth pathology characterized by deafness, vertigo, and tinnitus.[1] Patient with Meniere's disease may have an unpredictable prognosis and attacks could come more frequently and more severely, less frequently and less severely, and anywhere in between.[2] It can occur in anyone especially in people in their 40s, obesity, migraine, carbohydrate dysmetabolism, fat maldistribution, and hypertension.[1,3,4] Many hypotheses have been postulated for the possibility of the etiology of the disease, for instance including the vascular impairment from various causes affecting in the venous drainage of the inner ear.[2] Patients with type 2 diabetes, one of the most common systemic illness that affects vascular complication, had significantly higher incidence of hearing loss.[5] A previous study also mentioned that Meniere's syndrome associated with some conditions such as impaired glucose tolerance.[1] However, defining diabetes mellitus as the risk for Meniere's disease in hearing loss patient is still uncertain. Therefore the aim of the prsent study is to examine diabetes mellitus and risk for Meniere's disease in the patient with hearing loss.

METHODS

STUDY DESIGN AND PATIENTS

We conducted a hospital-based nested case–control study from Srinagarind Hospital, Khon Kaen, Thailand obtaining the data of patients visiting the hospital between January 2009 and December 2013 with a diagnosis associated with hearing loss. We excluded those aged younger than 15 years old, with congenital hearing loss, with missing data and with traumatic hearing loss. From the medical records, we identified 1,239 patients with hearing loss excluding 514 patients (Figure 1). From 721 patients; 287 with Meniere's disease (case-patient) and 434 without Meniere's disease (control patient), each case patient was matched 1:1 with age and gender to one control patient. Thus, the total patients left in the analysis were 574 patients.

DATA COLLECTION

Medical records of the eligible case and control patients were reviewed. Data prior to the initial treatment were retrieved and collected from patients' medical records. This included age, gender, body mass index (BMI), smoking status from the self-administered questionnaire, migraine, underlying disease e.g., hypertension, dyslipidemia and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Moreover, the results of audiogram of both ears for each patient were also recorded.

STATISTICAL ANALYSIS

All data were cleaned before all of the statistical analysis. For descriptive statistics, categorical variables were described using frequency (number and percentage) and continuous variables were described using median and interquartile range (IQR) for non-normally distributed data.

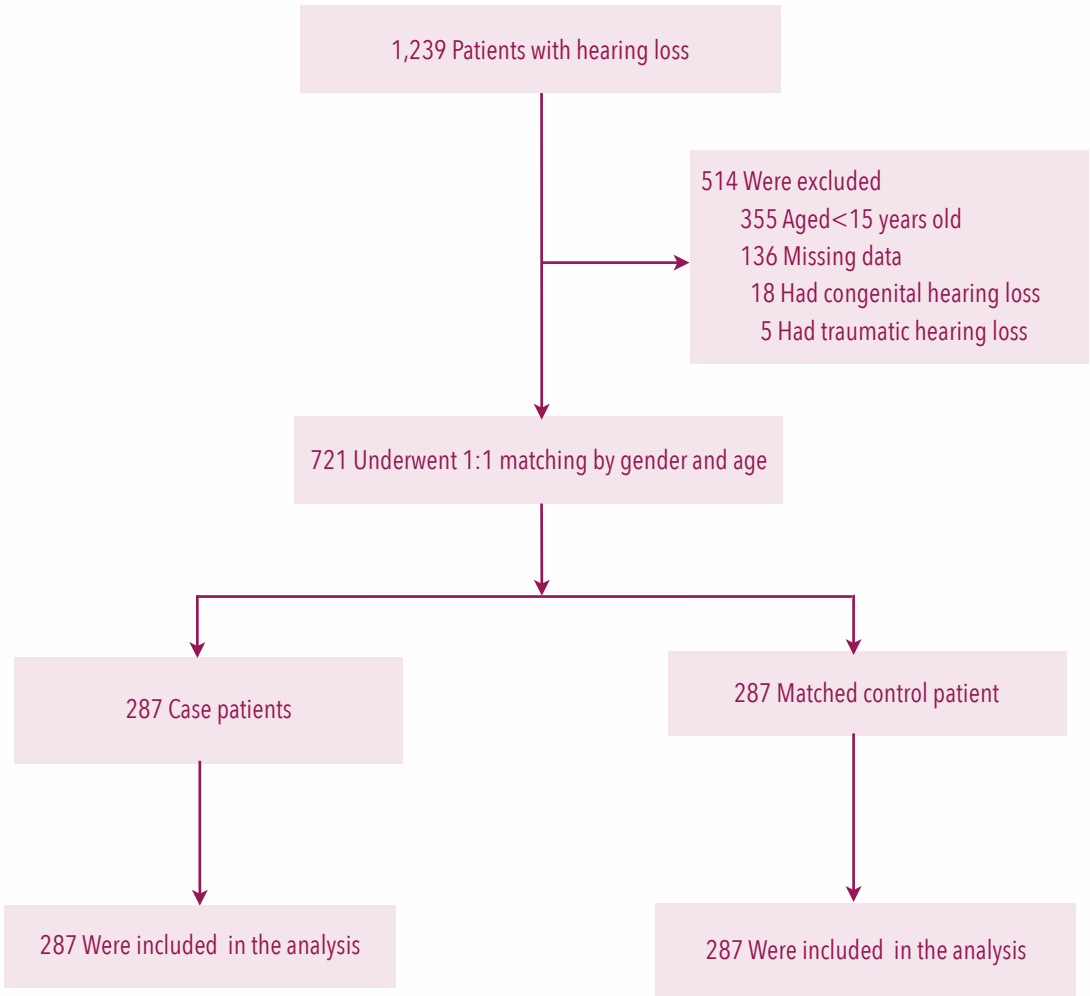

Figure 1. Study flow

Characteristics of case and control patients were compared with the use of the chi-square test for categorical variables and Mann-Whitney U test for continuous variables. We used crude odds ratio (COR) to estimate the proportional increase in the rate for the comparison of having Meniere's disease in the patient with hearing loss. Binary logistic regression models were constructed to identify independent risk factors associated with Meniere's disease. A two-sided P, 95% confidence interval (CI) and adjusted odds ratio (AOR) were used to denote the statisticcal significance.

Table 1. Characteristics of the patients

Characteristic	Hearing loss and Meniere's disease (n=287)	Hearing loss alone (n=287)	P Value
Age-yr			0.268
Median	53.3	54.7	
Interquartile range	47.8-60.6	47.9-62.2	
Male gender-no. (%)	115 (40.1)	115 (40.1)	1.000
Body-mass index*			0.005
Median	23.7	22.7	
Interquartile range	21.2-26.5	20.5-25.5	
Smoking status-no. (%)			0.127
Non-smoker	136 (91.3)	108 (87.1)	
Former smoker	9 (6.0)	6 (4.8)	
Current smoker	4 (2.7)	10 (8.1)	
Migraine-no. (%)	13 (4.5)	2 (0.7)	0.004
Psychiatric disorder-no. (%)	5 (1.7)	0	0.061
Underlying disease-no. (%)			
Diabetes mellitus	28 (9.8)	30 (10.5)	0.782
Hypertension	66 (23.0)	57 (19.9)	0.360
Dyslipidemia	19 (6.6)	13 (4.5)	0.275
Rheumatoid arthritis	0	3 (1.0)	0.249
Systemic lupus erythematosus	0	1 (0.3)	1.000
Vertigo-no. (%)	140 (48.8)	43 (15.0)	<0.001
Tinnitus-no. (%)	138 (48.1)	88 (30.7)	<0.001
Type of hearing loss no.-(%)			
Unilateral left conductive	17 (5.9)	30 (10.5)	0.048
Unilateral left sensorineural	64 (22.3)	22 (7.7)	<0.001
Unilateral left mixed	8 (2.8)	25 (8.7)	0.002
Unilateral right conductive	6 (2.1)	26 (9.1)	<0.001
Unilateral right sensorineural	58 (20.2)	23 (8.0)	<0.001

Table 1. (Continued)

Characteristic	Hearing loss and Meniere's disease (n=287)	Hearing loss alone (n=287)	P Value
Unilateral right mixed	4 (1.4)	7 (2.4)	0.361
Bilateral conductive	14 (4.9)	24 (8.4)	0.093
Bilateral sensorineural	94 (32.8)	56 (19.5)	<0.001
Bilateral mixed	7 (2.4)	25 (8.7)	0.001
Left conductive and right sensorineural	2 (0.7)	9 (3.1)	0.033
Left conductive and right mixed	4 (1.4)	3 (1)	0.725
Left sensorineural and right conductive	4 (1.4)	5 (1.7)	0.752
Left sensorineural and right mixed	2 (0.7)	13 (4.5)	0.004
Left mixed and right conductive	0	2 (0.7)	0.499
Left mixed and right sensorineural	1 (0.3)	18 (6.3)	<0.001
Air conduction of right ear-dB			0.012
Median	22	25	
Interquartile range	13-40	15-45	
Air conduction of left ear-dB			0.002
Median	25	37	
Interquartile range	17-42	18-53	
Bone conduction of right ear-dB			0.656
Median	20	22	
Interquartile range	13-38	13-33	
Bone conduction of left ear-dB			0.758
Median	22	22	
Interquartile range	15-35	15-35	

*The body-mass index is the weight in kilograms divided by the square of the height in meters.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Of the 574 included in the analysis. Most of them were female and their median age was 54.4 years (IQR 47.9 to 61.8), and their median BMI was 23.3 kg/m^2 (IQR 20.8 to 26.0). Table 1 shows patients' characteristics of case and control patients in more detail. The information regarding types of hearing loss between the two groups is also presented in

Table 2. Odds Ratios for Meniere's Disease Associated with Diabetes Mellitus and Other Characteristics.

Variable	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Diabetes mellitus	0.93 (0.54-1.60)	0.84 (0.46-1.52)
Male gender	1.00 (0.72-1.40)	1.05 (0.74-1.49)
Age-yr		
15-29	1	1
30-39	1.18 (0.38-3.63)	1.19 (0.37-3.79)
40-49	1.09 (0.40-2.92)	1.08 (0.39-3.02)
50-59	1.04 (0.40-2.72)	0.10 (0.37-2.71)
60-69	0.90 (0.33-2.47)	0.83 (0.29-2.38)
>70	0.78 (0.27-2.22)	0.72 (0.24-2.18)
Body mass index-kg/m^2	1.06 (1.02-1.10)	1.05 (1.01-1.09)
Hypertension	1.21 (0.81-1.80)	1.28 (0.81-2.02)
Dyslipidemia	1.49 (0.72-3.09)	1.44 (0.68-3.03)

Table 1. Generally, the characteristics of case and control patients were similar in relation to age, gender, smoking status, psychiatric disorder, underlying disease e.g., hypertension, dyslipidemia and autoimmune disease (rheumatoid arthritis, SLE), however, comparing between case and control, it found that the former tended to have higher BMI (P=0.005), higher proportion of patients with migraine (P=0.004), higher proportion of patients with vertigo (P<0.001) and higher proportion of patients with tinnitus (P<0.001).

From Table 2, COR and AOR of potential risk factors of having Meniere's disease are presented and they go in the similar direction. It found that diabetes was not associated with Meniere's disease; 10.5% in controls and 9.8% in cases (AOR, 0.84; 95% CI, 0.46 to 1.52). Moreover, male gender, age, hypertension, and dyslipidemia; were not associated with having Meniere's disease. However, higher BMI was associated with having Meniere's disease in patients with hearing loss (AOR, 1.05; 95% CI, 1.01 to 1.09).

For the subgroup analysis of case and control patients with diabetes, COR and AOR of potential risk factors for Meniere's disease are presented in Table 3. It found that serum level of HbA1c, age, and diabetic treatment were not significantly associated with having Meniere's disease. Details of the level of conductions of both ears in the patients with and without diabetes mellitus in these present study are shown in Table 4. In relation to comparing between patients with type 2 diabetes mellitus (58 patients) and patients without diabetes mellitus (516 patients), we found that the former group tended to have higher

Table 3. Subgroup analysis of the patients with diabetes.

Variable	Case patient with diabetes (n=28)	Control patient with diabetes (n=30)	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
HbA1c-mg%			0.83 (0.64-1.07)	0.82 (0.61-1.08)
Median	6.8	7.8		
Interquartile range	6.2-7.7	6.5-9.2		
Age-yr	60.4±8.9	60.0±12.7	1.00 (0.96-1.05)	1.00 (0.95-1.06)
Diabetic treatment-no. (%)				
Metformin	13 (46.4)	15 (50.0)	0.87 (0.31-2.43)	1.11 (0.24-5.18)
Sulfonylurea	6 (21.4)	10 (33.3)	0.55 (0.17-1.77)	0.37 (0.07-1.83)
Insulin	3 (10.7)	6 (20.0)	0.48 (0.11-2.14)	0.47 (0.08-2.83)
Diet control	3 (10.7)	3 (10.0)	1.08 (0.20-5.85)	0.82 (0.12-5.41)

Table 4. Level of conductions of the patients with and without diabetes mellitus.

Variable	Patients with diabetes mellitus (n=58)	Patients without diabetes mellitus (n=516)	P Value
Air conduction of right ear-dB			0.044
Median	36	23	
Interquartile range	17.75-50.5	13.5-43	
Air conduction of left ear-dB			0.178
Median	37.5	27	
Interquartile range	18-48.5	17-47	
Bone conduction of right ear-dB			0.005
Median	30	20	
Interquartile range	18-45	13-35	
Bone conduction of left ear-dB			0.008
Median	26	22	
Interquartile range	19.5-40	15-34.5	

severity in air conduction of right ear (P=0.044), bone conduction of right (P=0.005) and left ear (P=0.008)

DISCUSSION

IMPORTANT FINDINGS

Our study presents data from large numbers of the patient with hearing loss visiting Srinagarind Hospital, Khon Kaen, Thailand. Various risk factors for having Meniere's disease are presented. It found that diabetes mellitus was not a risk factor for Meniere's disease. Moreover, gender, age, hypertension, and dyslipidemia were also found not to be risk factors for Meniere's disease. In contrast, higher BMI modestly increased the risk a risk factor for Meniere's disease in patients with hearing loss. In the subgroup of those with diabetes, HbA1c, age, and treatment of diabetes mellitus were not found to be associated with having Meniere's disease as well.

COMPARISON TO PREVIOUS STUDIES

Due to the relatively rare of Meniere's disease in nature, the literature related to our findings then seems to be scarce.[6-8] In the present study, the most common age group of patients with Meniere's disease is 50 to 59, however, the prior study that conducted in Otolaryngologic Clinics of North America showed found patients with Meniere's disease in the younger age.[3] This minimal difference might be due to the different geographies and races. The result of present study found that diabetes mellitus was not a risk factor of having Meniere's disease which fail to reject our hypothesis that diabetes was a risk factor for Meniere's disease as we believed that diabetes is one of the common causes of arterial impairment that would lead to developing the disease as mention in the Italian study in 2013 using data on 32 cases stating that hemodynamic changes were observed in patients with Meniere's disease.[2] However, with the larger sample with more precise estimation of the relationship between diabetes and the disease in our study, our findings, thus, imply no or very small relationship of diabetes and Meniere's disease.

Although we found the difference from the prior studies compared with present study described as above, we found the similar conclusion in term of a migraine and BMI; in the current study showed a higher proportion of migraine in patients with Meniere's disease. Likewise, another study from the US in 2013 reported that migraine as a vascular risk factor for Meniere's attack.[9] We also found the association between Meniere's disease and higher BMI, as well as, a German study stated that BMI was a comorbidity of Meniere's disease.[10] We found that the those with diabetes tended to have higher severity of air and bone conductions. In similar direction of the result from the previous study conducted in McGill University, Montreal, Canada, in 2013 that reported patients with type 2 diabetes had significantly higher incidence for at least the mild degree of hearing loss.[5]

STRENGTHS AND LIMITATIONS

To our knowledge, this is the first study and the largest number of cases to directly identify the risk for Meniere's disease in the patient with hearing loss related to diabetes mellitus. The strengths of this study include the use of a hospital-based setting with adequate sample size and various confounding factors that cause Meniere's disease were thoroughly identified including detailed information of hearing loss was collected from the audiogram of all patients. The present study is also the first study exploring the relationship between the level of diabetic control, treatment, and risk for Meniere's disease.

Our study has several limitations owing to its retrospective design, including the risk of ascertainment, and confirmation, as well as missing data such as self-reported smoking status and history of sound exposed which were not validated by history taking and interview. Furthermore, we cannot control patients self-care that effects to the hearing status. Moreover, studies supported our findings are relatively scant.

CONCLUSIONS AND IMPLICATIONS

Diabetes mellitus is a disease that can cause vascular impairment and our study was designed to find the association between diabetes mellitus and risk for Meniere's disease. The results of this study suggested that there was no association between diabetes mellitus and risk for Meniere's disease. However, we suggest a prospective larger cohort should be conducted to ascertain this relationship.

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Types of membrane rupture and the length of the third stage of labor

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To investigate the relationship between types of membrane rupture and length of the third stage of labor.

METHODS

We conducted a retrospective cohort study to compare the length of the third stage of labor between two types of membrane rupture; artificial rupture of membrane (ARM) and spontaneous membrane rupture (SMR) in pregnant women undergoing normal labor from December 2011 to June 2012.

RESULTS

There were 1,001 pregnant women undergoing normal labor between the study period included in the analysis; 510 women in the group of ARM and 491 women in the group of SRM. The median length of the third stage of labor in the ARM group was similar to that of the SMR group; 4.5 minutes in ARM group and 4 minutes in SRM group ($P=0.483$). The median of the first stage of labor in the ARM group was longer than that of the SMR group; 510 minutes in the ARM group and 420 minutes in the SMR group ($P<0.001$). The median length of the second stage of labor in the ARM group was similar to that of SMR group; 14 minutes in the ARM group and 13 minutes in the SRM group ($P=0.245$). The median of the total length of labor, that resulted from summation the length of the first, second and third stages, in the ARM group was longer significantly; 529 minutes in the ARM group and 453 minutes in the SMR group ($P<0.001$). Moreover, there were no significantly differences in the estimated blood loss, maternal fever, APGAR score less than 7 at 1, 5 and 10 minutes and neonatal death comparing between the two groups.

CONCLUSION

ARM had the similar length of the third stage of labor to that of SRM. However, it had longer the first stage of labor significantly.

INTRODUCTION

Amniotomy or artificial ruptured membrane is a common obstetrical procedure.[1,2] When amnion is ruptured, it releases prostaglandin and other substance that it is one of the factors which makes uterus more contraction and cervix more dilatation.[3,4,5,6] Amniotomy can be both benefits and risks; it can reduce the length of the second stage of labor in nulliparous while it also reduces the amniotic volume which may cause cord compression.[7] Moreover, a previous study had stated that it may lower the infants' APGAR score less than 7 at 5 min in nulliparous women.[8] However, there is no evidence of serious complication such as perinatal death, respiratory distress syndrome and intracranial hemorrhage from amniotomy.[8]

Amniotomy seems to associate with labor time such as in the second stage. However, it is still inconclusive. Moreover, there was no study comparing the length of the third stage of labor or (time of placental delivery) between two types of amniotomy; artificial rupture of membrane (ARM) and spontaneous membrane rupture (SMR). We, thus, aimed to evaluate this relationship in the present study.

METHODS

STUDY DESIGN

Our study is designed as a retrospective cohort study to compare the length of the third stage of labor (time of placental delivery) between ARM and SMR.

STUDY SITE AND PATIENTS' RECORDS

Medical records of women with a singleton pregnancy with spontaneous onset of labor in cephalic presentation with intact membrane were selected and reviewed. Those with prolonging premature rupture of membrane, premature rupture of membrane, severe preeclampsia, death fetus in utero, malpresentation, birth before assist, twins and incomplete data were excluded. Then patients were classified into two groups; ARM group and SMR group.

STUDY OUTCOMES

The primary outcome was the length of the third stage of labor. The secondary outcomes were the length of the first and the second stage of labor and include both maternal and neonatal outcomes; postpartum hemorrhage, maternal fever, APGAR score<7 at 1,5,10 min, neonatal death.

DATA COLLECTION

Maternal and neonatal data were retrospectively collected by reviewing of their admission records from Obstetrics & Gynecology Department, Khon Kaen Hospital, Thailand between December 2011 and June 2012. Their characteristics included age, gestational age, gravida, parity, nulliparous, previous abortion, maternal weight, maternal height, cervical dilatation at admission, cervical dilatation at membrane rupture, gestational diabetes mellitus (GDM) of both types (A1 and A2), pregnancy-induced hypertension, oxytocin augmentation, prostaglandin E intravaginal, oxytocin during delivery, methylergometrine

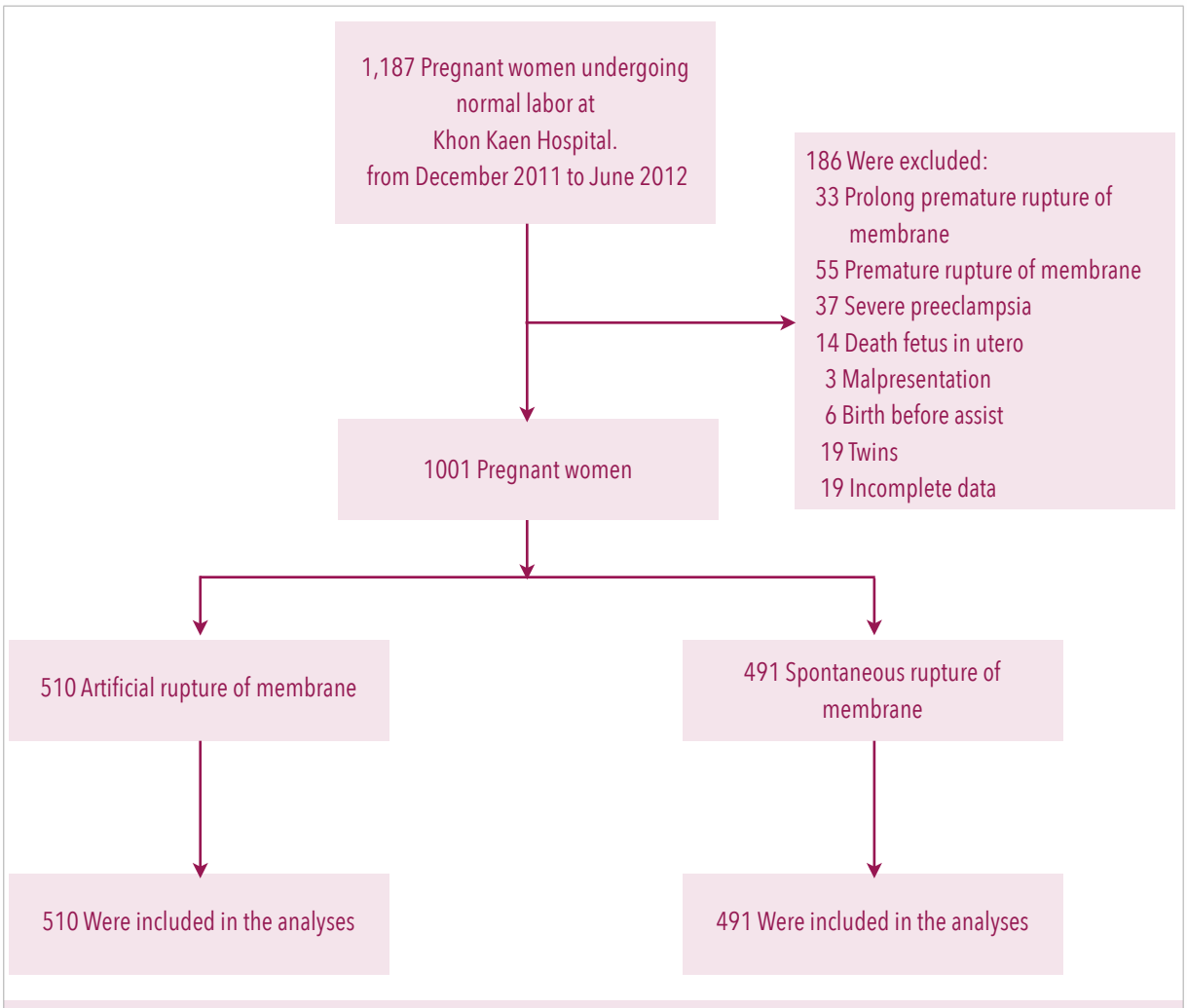

Figure 1. Study flow chart

maleate intravenous (IV) and oxytocin intramuscular (IM) or intravenous (IV) in postpartum, amniotic fluid, birth weight, method of delivery, episiotomy, degree of perineum tear and anesthesia.

Statistical analysis

All data were corrected by doing double entry before all analyses. All statistical analyses were done using the statistical software package such as EpiInfo7. Categorical variables were described as number and percentage. Between the two groups, all categorical variables were compared by using Pearson's Chi-square test. All numerical data were tested for their distribution by using Kolmogorov-Smirnov test. The non-normally distributed data of baseline characteristics of the mothers and the newborns were expressed as the

Table 1. Characteristics of the patients

Characteristic	ARM (n=510)	SRM (n=491)	P Value
Maternal age-yr			0.008
Median	23	25	
Interquartile range	20-28	20-29	
Gestational age-wk			<0.001
Median	39	38	
Interquartile range	38-40	37-40	
Gravida-no. (%)			0.036
Median	1	2	
Interquartile range	1-2	1-2	
Parity-no. (%)			0.331
Median	0	0	
Interquartile range	0-1	0-1	
Nulliparous-no. (%)	253 (49.6)	220 (44.8)	0.128
Previous abortion-time			0.072
Median	0	0	
Interquartile range	0	0	
Maternal weight-kg			0.459
Median	64.8	64	
Interquartile range	58.0-71.9	58-72	
Maternal height-cm			0.732
Median	158	158	
Interquartile range	154-161.3	154-161	
Cervical dilatation at admission-cm			0.038
Median	3	4	
Interquartile range	2-5	2-7	
Cervical dilatation at membrane rupture-cm			0.04
Median	6	7	
Interquartile range	4-8	4-10	
gestational diabetes mellitus-no. (%)			0.752
gestational diabetes mellitus type A1	3 (0.6)	5 (1.0)	
gestational diabetes mellitus type A2	5 (1.0)	4 (0.8)	
Pregnancy induced hypertension-no. (%)	9 (1.8)	15 (3.1)	0.182
Oxytocin augmentation-no. (%)	127 (24.9)	88 (17.9)	0.007
Prostaglandin E intravagina-no. (%)	35 (6.9)	55 (11.2)	0.016

Table 1. (Continued)

Characteristic	ARM (n=510)	SRM (n=491)	P Value
Oxytocin during delivery-no. (%)	218 (42.7)	142 (28.9)	<0.001
Methylergometrine maleate IV at postpartum -no. (%)	11 (2.2)	10 (2.0)	0.894
Oxytocin IM at postpartum-no. (%)	187 (36.7)	221 (45.0)	0.007
Oxytocin IV at postpartum-no. (%)	314 (61.6)	262 (53.4)	0.009
Amniotic fluid-no. (%)			0.538
Clear	422 (82.7)	417 (84.9)	
Mild meconium	47 (9.2)	36 (7.3)	
Thick meconium	41 (8.0)	38 (7.7)	
Birth weight(g)			<0.001
Median	3,070	3,000	
Interquartile range	2,820-3,312.5	2,690-3,250	
Method of delivery-no. (%)			0.419
Spontaneous	478 (93.7)	466 (94.9)	
Vacuum	32 (6.3)	25 (5.1)	
Episiotomy-no. (%)			<0.001
None	74 (14.5)	111 (22.6)	
Median episiotomy	8 (1.6)	14 (2.9)	
Right mediolateral episiotomy	427 (83.7)	360 (73.3)	
Left mediolateral episiotomy	1 (0.2)	6 (1.2)	
Degree of perineum tear-no. (%)1			0.112
No perineum tear	21 (4.1)	31 (6.3)	
First degree tear	463 (90.8)	427 (87.0)	
Second degree tear	18 (3.5)	27 (5.5)	
Third degree tear	7 (1.4)	3 (0.6)	
Fourth degree tear	1 (0.2)	3 (0.6)	
Anesthesia-no. (%)			0.262
None	38 (7.5)	50 (10.2)	
Local anesthesia	462 (90.6)	434 (88.4)	
Pudendal nerve block	10 (2.0)	7 (1.4)	

median and interquartile range (IQR) and compared using Mann-Whitney U test. Potential risk factors were interpreted as odds ratio (OR) and its 95% confidence intervals (CI). Kaplan-Meier Curves and Log-Rank test were used to identify variables that may confound the outcomes.

Table 2. Outcomes

Outcome	ARM (n=510)	SRM (n=491)	Hazard ratio	95%CI	P Value
Third stage of labor-min					0.483
Median	4.5	4			
Interquartile range	3-6	3-6			
First stage of labor-min					<0.001
Median	510	420			
Interquartile range	333.8-716.3	280-650			
Second stage of labor-min					0.245
Median	14	13			
Interquartile range	9-23	7-21			
Total of labor-min					<0.001
Median	529	453			
Interquartile range	360.0-733.5	298-672			
Maternal outcome					
Estimate blood loss-ml.					0.647
Median	150	150			
Interquartile range	150-150	150-150			
Fever	19 (3.7)	20 (4.1)	0.91	(0.48-1.73)	
Neonatal outcome					
APGAR score<7-no. (%)					
1 min	12 (2.4)	23 (4.7)	0.49	(0.24-1.00)	
5 min	1 (0.2)	6 (1.2)	0.16	(0.02-1.32)	
10 min	0	4 (0.8)	NA	NA	
Death-no. (%)	0	3 (0.6)	NA	NA	

RESULTS

There were 1,187 pregnant women who undergoing normal labor delivery during December 2011 to June 2012. One hundred and eighty-six pregnant women were excluded (Figure 1). In total, 1,001 pregnant women and their children were left for the analysis. Pregnant women were separated into two groups, 510 women in the ARM group and 491 women in the SMR group.

The baseline of characteristics was generally similar between the two groups (Table 1). However, those in the ARM group tended to have higher gestational age (P<0.001), less gravida (P=0.036), higher proportion of nulliparous (P=0.128), greater maternal body weight (P=0.459), less cervical dilatation at

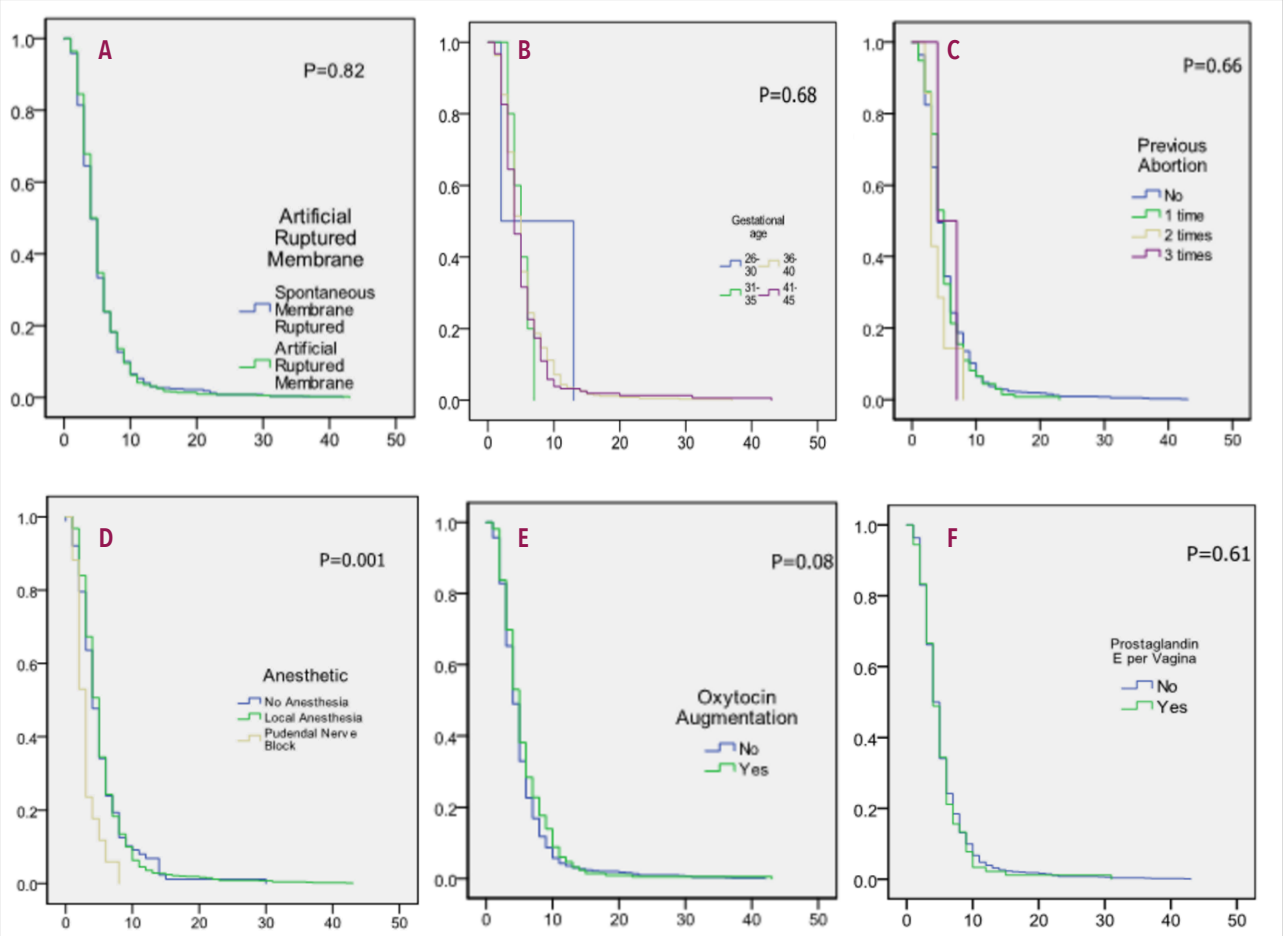

Figure 2. Kaplan–Meier Curves showing the proportion of the relationship between potential confounder and the length of the third stage of labor.

X axis is length of the third stage of labor and Y axis is cumulative incidence of placenta delivery.

Panel A, the association between types of membrane rupture and the outcome; Panel B, the association between gestational age and the outcome; Panel C, the association between history of previous abortion and the outcome; Panel D, the association between type of anesthesia and the outcome; Panel E, the association between oxytocin augmentation and the outcome and; Panel F, the association between using prostaglandin E per vagina and the outcome.

admission (P=0.038) and at membrane rupture (P=0.040), less proportion of GDMA1 and higher proportion of GDMA2 (P=0.752), less proportion of pregnancy induced hypertension (P=0.182), higher proportion of those prescribed oxytocin (P=0.007), less proportion of prostaglandin E intravaginal (P=0.016), higher proportion of oxytocin during delivery (P<0.001), higher proportion of those prescribed methylergometrine maleate IV at postpartum (P=0.894), less

proportion of those prescribed oxytocin IM at postpartum (P=0.007), higher proportion of those prescribed oxytocin IV at postpartum (P=0.009), higher proportion of clear, mild and thick meconium fluid (P=0.538), greater neonatal birth weight (P<0.001), less proportion of those with spontaneous delivery but higher vacuum delivery (P=0.419), less proportion of those with no episiotomy, median and left mediolateral episiotomy but higher proportion of right mediolateral episiotomy (P<0.001), higher proportion of perineum tear (P=0.112), higher proportion of local and pudendal anesthesia and fewer proportion in non-anesthetic use (P=0.262).

From Table 2, The median length of the third stage of labor in the ARM group was similar to that of the SMR group; 4.5 minutes in ARM group and 4 minutes in SRM group (P=0.483). The median of the first stage of labor in the ARM group was longer than that of the SMR group; 510 minutes in the ARM group and 420 minutes in the SMR group (P<0.001). The median length of the second stage of labor in the ARM group was similar to that of SMR group; 14 minutes in the ARM group and 13 minutes in the SRM group (P=0.245). The median of the total length of labor, that resulted from summation the length of the first, second and third stages, in the ARM group was longer significantly; 529 minutes in the ARM group and 453 minutes in the SMR group (P<0.001). Moreover, there were no significantly differences in the estimated blood loss, maternal fever, APGAR score less than 7 at 1, 5 and 10 minutes and neonatal death comparing between the two groups. From the Kaplan–Meier analysis (Figure. 2) to identify factors that might affect the length of the third stage of labor, we found that in pudendal nerve block shortened the length of the third stage of labor compared with no anesthetic used and local anesthesia (P=0.001).

DISCUSSION

In this retrospective cohort study, we found the length of the third and the second stage of labor was similar in both ARM and SMR group. The length of the first stage of labor in ARM group was longer to that of SMR group significantly as well as the total length of labor. However, there were no significantly differences in estimated blood loss, maternal fever, APGAR score less than 7 at 1,5,10 minutes and neonatal death comparing between the two groups.

STRENGTH AND LIMITATION

The strength of this study is that we are the first study that mentioned the association between the length of the third stage of labor and types of membrane ruptured. We collected data by reviewing the admission record especially the labor noted in a checklist form, many details were noted completely and correctly. The main limitation of our study is an inability to perform formal evaluation for all subjects. However, we collected data from admission records which data in the records were noted by many people, this tended to have errors from information bias. Secondly, although the sample size was underpower from statistical program calculation, we included up to one thousand records of the pregnant women and their children in Northeastern Thailand which might represent

some parts of the population. Thus, worldwide study should be performed to figure out the better answer for worldwide population. Thirdly, patients who had an amniotic membrane leakage and ended up with ARM, we classified them to the ARM group that they might not actually be in the ARM group. Fourthly, Although our study showed no anesthetic used and local anesthesia tend to increase the length of the third stage of labor when compared with pudendal nerve block, but in our the hospital practice, they used it after the newborns and placentas were past from perineum, so that types of anesthesia cannot affect to the length of the third stage of labor.

COMPARISON WITH OTHER STUDIES

Our study was concluded that no significant differences of the length of the third stage of labor between ARM and SMR by median of the length of third stage labor, 4.5 minutes (IQR, 3 to 6) in ARM group and 4 minute (IQR, 3 to 6) in SRM group. However, there is no study interesting about the length of the third stage of labor between ARM and SMR. The median of the length of the first stage of labor, our study was presented 510 minutes (IQR, 333.8 to 716.3) in ARM group and 420 minute (IQR, 280 to 650) in SRM group (P<0.001), which contrast with the systematic review from Cochrane Collaboration reporting that the mean difference and 95% CI of the length of the first stage of labor in ARM group was similar with that of SMR, -0.30 (-1.13 to 0.53).[8] It might be result of some confounders in ARM or SMR group that effected the first stage of labor that we did not find. The median of the length of the second stage of labor, we found 14 minutes (IQR, 9 to 23) in ARM group and 13 minute (IQR, 7 to 21) in SRM group (P=0.245). This also contrast with the systematic review from Cochrane Collaboration showing that the mean difference and 95% CI of the length of the second stage of labor in nulliparous of both group are -6.59 (-12.34 to -0.84).[8] However, our study has larger population, it about one thousand people but in the systematic review from Cochrane Collaboration, total number of people of their study is 496 peoples, so our study can represent the greater result than them. For the neonatal outcomes, our results support previous prospective randomized study which described no difference in the number of babies with poor APGAR scores between two group.[12] However, our study shows different result from recent systematic review from Cochrane Collaboration which showed the relative risk and 95% CI that APGAR score<7 at 5 minutes in ARM group with nulliparous had a large number of baby compared with SMR group is 0.42 (0.20 to 0.88).[8] It contrasts with our study that only one baby were shown in ARM group and 6 babies in SMR group (COR, 0.16; 95% CI, 0.02 to 1.32). However, we studied only about a thousand samples that might not be enough to represent the great answer.

CONCLUSION AND IMPLICATION

In the final results, we found that there is no effect of ARM on the length of the third stage of labor. Moreover, ARM that often done in many hospitals

may not have a benefit in term of the length of labor and might prolongs the length of first stage of labor. Thus, amniotomy, should be performed in cases with proper indication. Further study may include other methods that can shorten the length of third stage labor such as membrane stripping or studying about type of anesthesia that affect the length of the third stage of labor.

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Previous cesarean delivery and fetal breech presentation in women undergoing cesarean delivery

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ABSTRACT

OBJECTIVE

To evaluate the relationship between pregnant women with previous cesarean delivery and breech presentation of their infants.

METHODS

Retrospective cohort study was conducted. Medical records of women undergoing cesarean delivery with a singleton pregnancy who delivered a live-born infant at Khon Kaen Hospital between April 2012 and February 2013 were evaluated. They were categorized into two groups; with and without history of previous cesarean delivery. The outcome was breech fetal presentation.

RESULTS

There were 968 cesarean delivery during the study period; 622 women had history of previous cesarean delivery and 346 women had no history of cesarean delivery. It found that those with the history of previous cesarean delivery more than one time (AOR, 0.09; 95% CI, 0.02 to 0.41) and higher gestational age (AOR, 0.08; 95% CI, 0.72 to 0.88) tended to have less breech presentation newborn. However, maternal age, maternal height, pregravid weight, pre delivery weight, gravida, history of parity and history of vaginal delivery seemed to not associated with the breech presentation.

CONCLUSION

Mother undergoing cesarean delivery with history of previous cesarean delivery had more than one time had less infant with breech presentation.

INTRODUCTION

The rate of cesarean delivery rate has been significantly increasing from 11.3% in 1992 to 23.6% in 2011.[1] The main cause is likely to be associated with overdiagnosis of cephalopelvic disproportion and subsequent repeated cesarean section, while other indications play only a minimal role.[1] Maternal with a history previous cesarean section might have complication in following pregnancies including uterine rupture, preeclampsia, placental abruption, preterm birth, low birth weight, small for gestational age, stillbirth, unexplained stillbirth and breech presentation.[2-5] A study from Greece in more than 4,000 pregnant women in 2008 suggested that women with previous cesarean delivery tended to have a higher rate of breech presentation infants.[6] However, there are no others studies examining the association between history of previous cesarean delivery in women undergoing cesarean delivery and breech presentation of the infant, thus, with very few evidence, we aimed to evaluate this relationship through the present study.

METHODS

STUDY DESIGN AND OVERSIGHT

This is a retrospective cohort study examining the association between history of previous cesarean delivery in women undergoing cesarean delivery and breech presentation of the infant. This study was conducted in Khon Kaen Hospital, Thailand. Pregnant women undergoing cesarean delivery between April 2012 and February 2013 were all included. We excluded those with their first pregnancy, multiple pregnancies, fetal anencephaly, dead fetus in utero or incomplete data regarding primary outcome.

STUDY OUTCOME

The primary outcome was the fetal breech presentation of the newborn and secondary outcomes were placenta previa, APGAR score of the infant<7 at 5 min, infant birth weight, spontaneous preterm birth and postpartum hemorrhage.

DATA COLLECTION

The primary outcome was the breech fetal presentation of the newborn and secondary outcomes were placenta previa, APGAR score of the infant<7 at 5 min, infant birth weight, spontaneous preterm birth and postpartum hemorrhage.

STATISTICAL ANALYSIS

All data were double entered and cleaned before preceding the analysis. All analyses were performed using the statistical software. All numeric variable were tested for their distribution using Kolmogorov-Smirnov (KS) test. Non-normal distributed data were expressed using median and interquartile range (IQR) for comparisons the baseline characteristics of the mothers and the newborns. We analyzed characteristics of the mothers that were related to the maternal history of previous cesarean delivery in each category

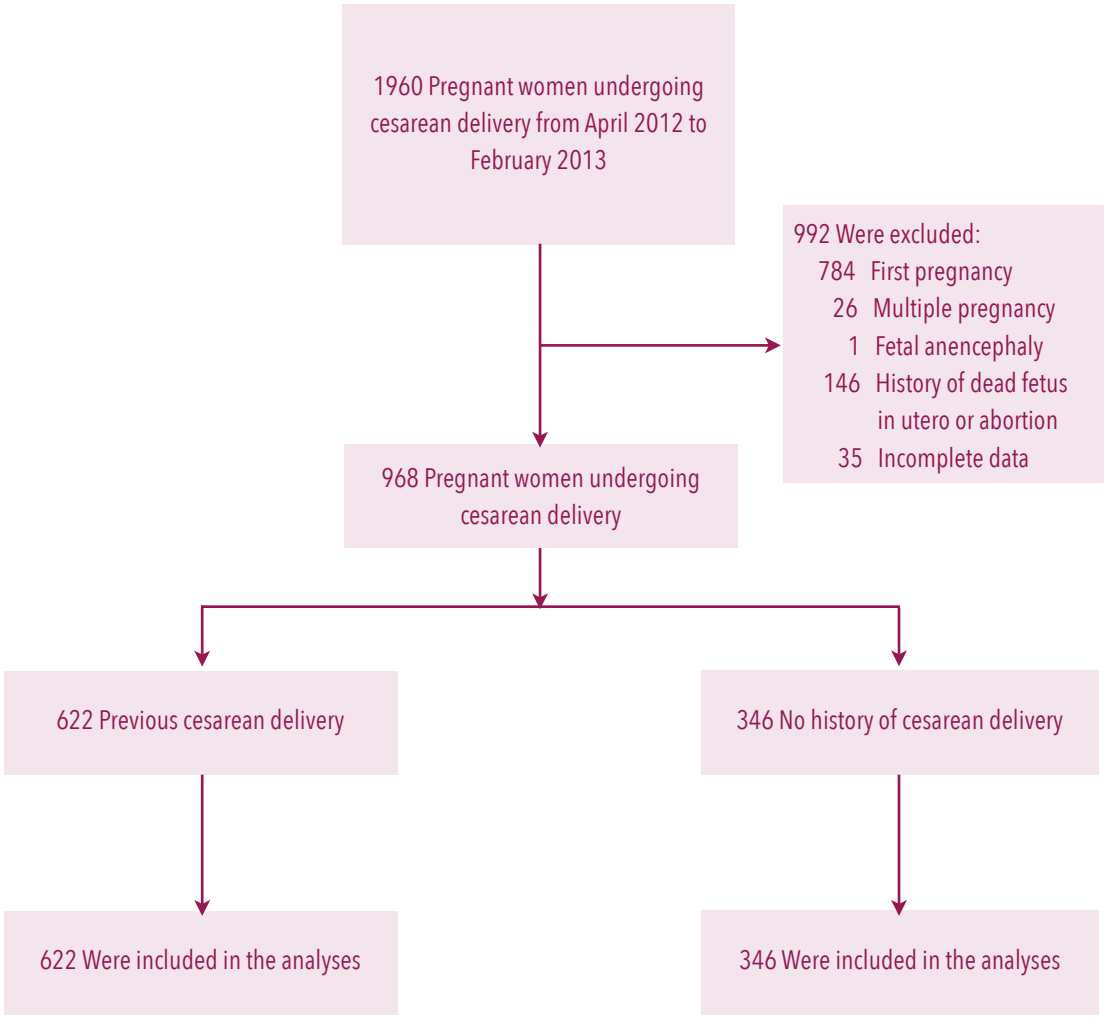

Figure 1. Study flow chart

using either Pearson's Chi-square or Fisher's exact test where appropriate if the data were categorical variables and we used Mann-Whitney U test if they were scale variables. All factors were analyzed for risk association using crude odds ratio (COR) and its 95% confidence intervals (CI). To adjust for possible potential confounders of the outcomes, the binary logistic regression analysis was performed to calculate adjusted odds ratio (AOR) and its 95% CI.

RESULTS

PATIENTS

In Figure 1, a total of 1,960 pregnant women undergoing cesarean delivery were screened for eligibility, 992 pregnant women were excluded, 968 pregnant women who delivered by cesarean section were included. They were organized into two groups by the history of previous cesarean delivery; 622 women with a history of cesarean delivery and 346 women without a history of previous cesarean delivery. Their median age was 30 years old with the median gestational age of 38 weeks, other baseline characteristics of those who eligible are listed in Table I. Comparing to those without history of previous cesarean delivery, it seemed that patient with history of previous cesarean delivery tended to be younger ($P<0.001$), younger gestational age ($P<0.001$), taller ($P<0.017$), had more gravida ($P<0.001$), fewer term parity ($P<0.001$), fewer abortion ($P=0.031$), fewer live birth ($P<0.001$), fewer previous vaginal delivery ($P<0.001$), fewer fetal distress ($P<0.001$), fewer cephalopelvic disproportion ($P<0.001$), fewer placenta previa ($P<0.001$), and fewer hypertension in pregnancy ($P=0.024$). For the infant characteristics, comparing to the newborns of those without history of previous cesarean delivery, we found that the newborns from women with history of previous cesarean delivery were likely to weigh more ($P<0.001$) and better APGAR score at 1, 5 and 10 minutes ($P<0.001$, $P<0.001$ and $P<0.001$, respectively).

OUTCOMES

In the present study, mothers with history of previous cesarean delivery were found to have fewer breech presentation of the infant (COR, 0.05; 95% CI, 0.03 to 0.10), fewer placenta previa (COR, 0.01; 95%CI 0.03 to 0.28), lower proportion of infant birth weight less than 2,500 grams (COR, 0.61; 95% CI, 0.40 to 0.94) and more than 4,000 g (COR, 0.23; 95% CI, 0.12 to 0.45), fewer postpartum hemorrhage (COR, 0.47; 95% CI, 0.23 to 0.99). However, there were no significant differences comparing the two groups regarding other outcomes e.g., APGAR score<7 at 5 minutes, infant male sex, infant birth weight 2,500-4,000 g and spontaneous preterm birth.

FACTORS DETERMINING BREECH PRESENTATION

Table 3 presents factors predicting breech presentation of the newborns and placenta previa. It found that those with the history of previous cesarean delivery more than one time (AOR, 0.09; 95% CI, 0.02 to 0.41) and higher gestational age (AOR, 0.08; 95% CI, 0.72 to 0.88) tended to have less breech presentation newborn. However, maternal age, maternal height, pregravid weight, pre delivery weight, gravida, history of parity and history of vaginal delivery seemed to not associated with the breech presentation.

Moreover, it found that history of previous cesarean section one time (AOR, 0.06; 95% CI, 0.01 to 0.40) and history of abortion (AOR, 0.04; 95% CI, 0 to 0.64) are tended to have

Table 1. Characteristics of the patients

Characteristic	Previous cesarean delivery (n=622)	No previous cesarean delivey (n=346)	P Value
Maternal			
Age-yr			<0.001
Median	29	31	
Interquartile range	25-33	27-35	
Gestational age weeks -no. (%)			<0.001
Less than 37	69 (11.1)	46 (13.3)	
37 to 42	553 (88.9)	300 (86.7)	
Median	38	38	
nterquartile range	37-38	38-40	
Height-centimeters			0.017
Median	157	156	
Interquartile range	153-160	152-160	
Pregravid weight-kilograms			0.475
Median	55	55	
Interquartile range	49-63	48-62	
Pre Delivery weight-kilograms			0.745
Median	69	68	
Interquartile range	61.2-77.0	62-76	
Smoking -no. (%)	1 (0.2)	4 (1.2)	0.058
Alcohol drinking-no. (%)	1 (0.2)	3 (0.9)	0.133
Gravida-no. (%)			<0.001
=2	435 (69.9)	180 (52.0)	
>2	187 (30.1)	166 (48.0)	
Parity			
Term			< 0.001
Median	1	1	
Interquartile range	1-1	1-2	
Preterm			0.188
Median	0	0	
Interquartile range	0	0	

Table 1. (Continued)

Characteristic	Previous cesarean delivery (n=622)	No previous cesarean delivey (n=346)	P Value
Abort			0.031
Median	0	0	
Interquartile range	0	0-1	
Alive			<0.001
Median	1	1	
Interquartile range	1-1	1-2	
Previous vaginal delivery-no. (%)			<0.001
One	34 (5.5)	240 (69.3)	
Two	3 (0.48)	95 (27.4)	
Indications for repeat cesarean delivery-no. (%)			
Previous cesarean delivery	622 (100)	0	<0.001
Breech presentation	10 (1.6)	81 (23.4)	<0.001
Fetal distress	7 (1.1)	61 (17.6)	<0.001
Cephalopelvic disproportion	2 (0.3)	91 (26.3)	<0.001
Placenta previa	4 (0.6)	22 (6.4)	<0.001
Other indications*	11 (1.8)	41 (11.8)	<0.001
Underlying disease-no. (%)			
Thalassemia	8 (1.3)	8 (2.3)	0.23
Diabetes mellitus	39 (6.3)	26 (7.5)	0.458
Hypertension in pregnancy	19 (3.1)	21 (6.1)	0.024
Viral hepatitis	8 (1.3)	2 (0.6)	0.509
HIV infection	4 (0.6)	2 (0.6)	1.000
Others underlying disease	25 (4)	14 (4.0)	0.984
Neonatal			
Birth weight-kg			0.001
Median	3095	3215	
Interquartile range	2827.5-3352.5	2828.6-3570.0	
Male sex-no. (%)	326 (52.4)	196 (56.6)	0.205

*Other indications including fetal macrosomia.
Others underlying diseases including epilepsy , asthma , migraine , limb amputation , allergic rhinitis , anemia, thyroid disease and heart disease.

Table 2. Outcomes

Outcome	Maternal previous cesarean section (n=622)	No history of cesarean section (n=346)	Crude odds ratio (95% CI)
Primary outcome			
Breech presentation-no. (%)	10 (1.6)	81 (23.4)	0.05 (0.03-0.10)
Secondary outcome			
Placenta previa-no.	4 (0.6)	22 (6.4)	0.10 (0.03-0.28)
APGAR score<7 at 5 min	7 (1.1)	10 (2.9)	0.38 (0.14-1.01)
Infant birth weight-grams-no. (%)			
<2500	51 (8.2)	44 (12.7)	0.61 (0.40-0.94)
2500-4000	557 (89.5)	271 (78.3)	2.41 (1.68-3.47)
>4000	14 (2.3)	31 (9.0)	0.23 (0.12-0.45)
Spontaneous preterm birth	69 (11.1)	46 (13.3)	0.81 (0.55-1.21)
Postpartum hemorrhage	14 (2.3)	16 (4.6)	0.47 (0.23-0.99)

fewer placenta previa but higher gestational age (AOR, 7.77; 95% CI, 0.67 to 0.87) tended to have more placenta previa. However, maternal age, maternal height, pregravid weight, pre delivery weight, gravida, history of parity and history of vaginal delivery seemed to not associated with the breech presentation.

DISCUSSION

MAJOR FINDINGS

In this retrospective cohort study, we conducted two groups comparing the breech presentation of the infant in the history of previous cesarean delivery in women undergoing cesarean delivery and no history of previous cesarean delivery. The findings differed between the two groups. We found that breech presentation of the infant, placenta previa, postpartum hemorrhage, lower infant birth weight less than 2,500 g and more than 4,000 g were found fewer in mothers with the history of previous cesarean delivery significantly difference.

STRENGTH AND LIMITATION

A major strength of this study is that we studied from adequate sample size, completely collected data by retrieving and reviewing patient medical records.

However, our study is a retrospective cohort study, the missing data can not be recollected in medical records in some cases and many

Table 3. Factor predicting breech presentation and placeta previa

Factor	Breech presentation	Placenta previa
	Adjusted odds ratio (95% confidence interval)	
Previous history of cesarean delivery		
One time	0.09 (0.02-0.41)	0.06 (0.01-0.40)
Two times	0.09 (0)	0
Maternal age-years	1.00 (0.95-1.04)	1.02 (0.95-1.11)
Height-centimeters	1.00 (0.96-1.05)	1.07 (0.99-1.16)
Smoking	2.20 (0.10-48.45)	46.40 (1.73-1240.03)
Gestational age-weeks	0.80 (0.72-0.88)	7.77 (0.67-0.87)
Gravida	0.43 (0.08-2.37)	27.93 (1.63-478.53)
History of parity		
Term	1.85 (0.26-13.32)	0.05 (0-1.04)
Preterm	5.65 (0.78-41.03)	0.03 (0-1.02)
Abortion	2.51 (0.44-14.24)	0.04 (0-0.64)
Alive	1.10 (0.33-3.67)	1.87 (0.20-17.38)
Previous history of vaginal delivery		
One time	1.69 (0.38-7.53)	0.52 (0.08-3.48)
Two times	3.18 (0.33-30.26)	0.46 (0.04-6.01)
Three times	7.44 (0.23-238.68)	0.14 (0-13.26)
Four times	36.10 (0.19-6921.74)	N/A
Pregravid weight by predelivery weight	1.00 (0.98-1.00)	0.96 (0.99-1.00)
Pregravid weight	1.04 (0.87-1.23)	1.51 (1.01-2.26)
Pre delivery weight	1.07 (0.94-1.21)	1.24 (0.90-1.69)

confounding factors that hard to control with this type study such as maternal age, gestational age, maternal height, maternal pregravid weight and pre delivery weight, smoking, alcohol drinking, gravida, parity, history of vaginal delivery, history of cesarean delivery, maternal underlying disease these confounding factors could make error outcomes.

COMPARISON WITH OTHER STUDIES

The results of our study suggested that mothers with the history of previous cesarean or mothers that higher gestational age at delivery had less breech presentation of the infant that contrast with a study from Greece in 2008 which suggested that women with the history of previous cesarean delivery tended to have a

higher rate of breech presentation infants.[6] Furthermore, in this study, the number of previous cesarean delivery more one time correlate with breech presentation while the previous study is not statistically significant that the number of the previous cesarean delivery did not correlate with breech presentation.[6] However, there are no others studies examining the association between history of previous cesarean delivery in women undergoing cesarean delivery and breech presentation of the infant. Moreover, we also found that maternal with previous cesarean section are fewer low infant birth weight and high infant birth weight and more normal infant birth weight but there is no other study reveal its relation.

CONCLUSION AND IMPLICATION

In conclusion mothers with history of previous cesarean delivery had fewer breech presentation of the infant. Moreover, older gestational age tended to have fewer breech presentation of the infant as well. A larger prospective cohort study should be done to clarify this relationship.

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Benefits of thyroid hormone suppressive therapy for treatment of benign solitary thyroid nodule: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the benefit of thyroid hormone suppressive therapy for reducing nodule volume in patients with benign solitary thyroid nodule

METHODS

We performed a systematic review and meta-analyses. We searched using the electronic database and performed hand searching. We included only randomized controlled trials reporting effects of thyroid hormone suppressive therapy for reduction nodule volume comparing placebo or no treatment in the patient with the benign solitary thyroid nodule that followed up for six months or longer. The main outcomes were reduction of nodule volume more than 50% from baseline. Secondary outcomes were adverse reactions including headache, malaise, nervousness, and tachycardia.

RESULTS

Twelve randomized controlled trials including 736 participants were included for meta-analyses. The meta-analyses showed no benefits of thyroid hormone suppressive therapy for reducing thyroid nodule volume more than 50% from the baseline which followed up for 6 months (10.4% in the treatment group and 17.8% in control group; risk ratio=0.58; 95% CI [0.20 to 1.63]). However, for 12-month followed up, the thyroid hormone suppressive therapy had significant benefit for reducing thyroid nodule volume more than 50% from the baseline (27.3% in the treatment group and 11.9% in control group; risk ratio=2.25; 95% CI [1.51 to 3.35]). The adverse reaction in those with thyroid hormone suppressive therapy was also found more common compared to those in the control group. The evidence of the benefit of thyroid hormone suppressive therapy at 18-month follow-up or longer due to a limited number of the study.

CONCLUSION

Using of thyroid hormone suppressive therapy has the benefit of reducing benign thyroid nodule volume at 12 months of follow-up.

INTRODUCTION

Thyroid nodule is a common disease with the prevalence of palpable thyroid nodules of 4-7% of the US population and as high as 19-67% are accidentally found on ultrasonography.[1] Thyroid hormone suppressive therapy is controversial for treating benign solitary thyroid nodule. For instance, a meta-analysis in 2002 showed that thyroid hormone suppressive therapy has no significant benefit for reducing the volume of thyroid nodules.[2] However, in 2005, there was another meta-analysis that suggested thyroid hormone suppressive therapy can significantly reduce the volume of thyroid nodules.[3] Since then, there are numbers of randomized controlled trials regarding the use of thyroid hormone suppressive therapy in those with solitary thyroid nodule has been published.[4,5,6,7] One of these suggests thyroid hormone suppressive therapy can reduce the volume of thyroid nodules in some patient.[4] However the remaining suggest that no benefit for reducing the volume of the thyroid nodule.[5,6,7] Later in 2010, there was another meta-analysis suggested the superiority of thyroid hormone suppressive therapy for reducing the volume of the nodules over placebo or no treatment.[8] Nonetheless, this meta-analysis did not include the randomized controlled trials that mentioned above and its justification for conduct a meta-analysis was solely based on the previous meta-analyses in 2002.[8] Thus, the objective of the present systematic review is to identify the benefit of thyroid hormone suppressive therapy for reducing nodule volume in patients with benign solitary thyroid nodule.

METHODS

This is a systematic review to identify the effects of thyroid hormone suppressive treatment for reducing the volume of the thyroid nodule and it was conducted according to Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0.

SEARCH STRATEGIES

Four authors independently searched for online databases including Pubmed, Scopus, the Cochrane Library (any years-2013) for citations relevant to our research question by reviewing articles and abstract. We used a combination of MeSH for Pubmed searching ("thyroid nodule" AND "thyroxine") and used keyword "thyroid nodule AND thyroxine", "thyroid nodule AND levothyroxine", "thyroid nodule AND thyroid suppressive therapy" AND "thyroid nodule and thyroid hormone" in Scopus and the Cochrane Library. We checked the references of included studies for additional studies which were relevant. We did not restrict on language or publication year.

INCLUSION AND EXCLUSION CRITERIA

We included only randomized controlled trials reporting effects of thyroid hormone suppressive therapy comparing placebo or no treatment in the patient with a solitary benign thyroid nodule. The main outcome of our interest was volume reducing of thyroid nodule during follow-up more than six months. Secondary outcomes were side effects (nervousness, malaise, osteoporosis, cardiac side effects), serum thyroid stimulating hormone and T4 level, thyroid cancer incidence.

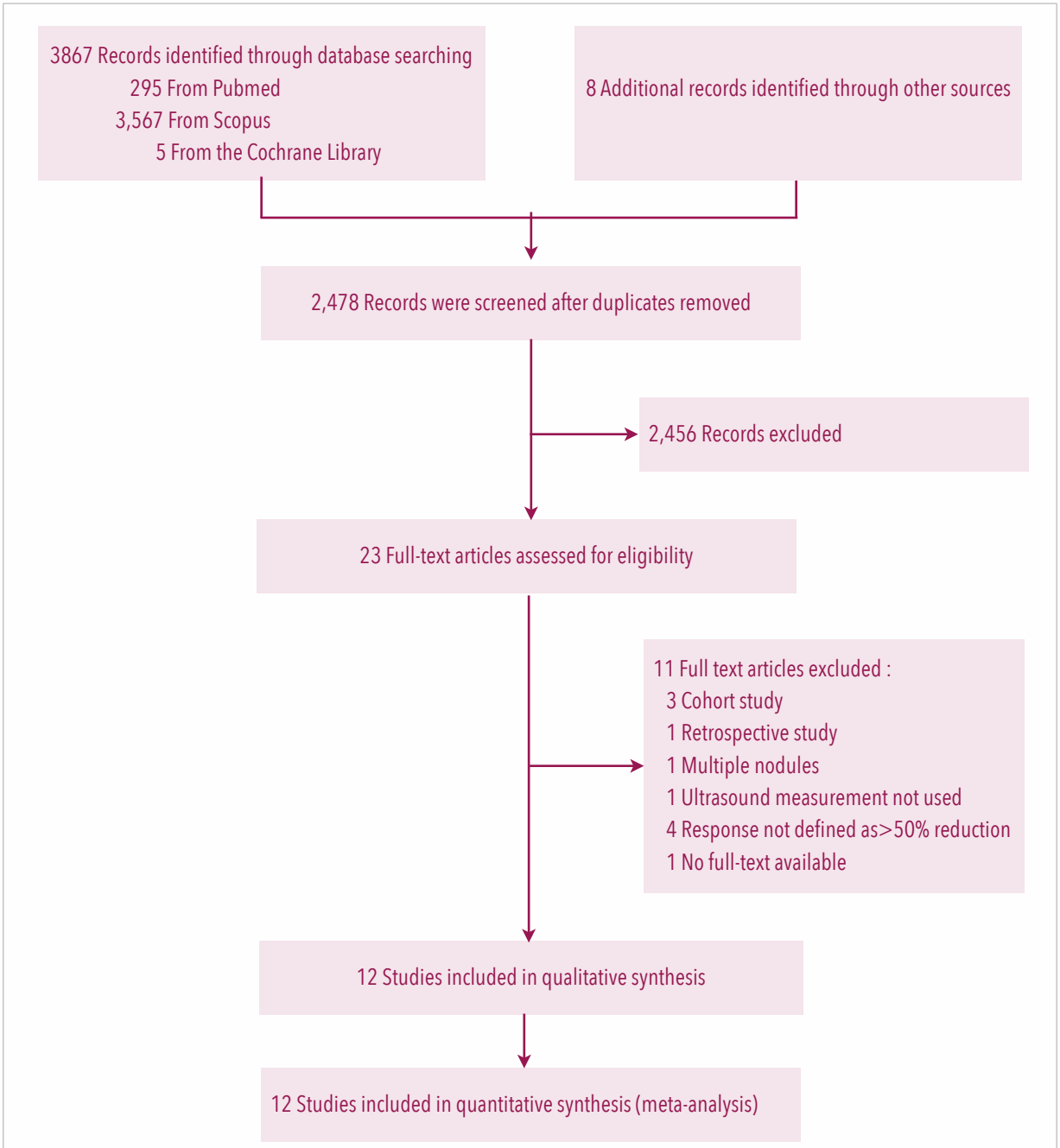

Figure 1. Study flow diagram

Table 1. Characteristic of included studies

No.	Author	study design	No. (female)	Age-years	Diagnosis	TSH level -mIU/mL	Initial dose of levothyroxine	Duration -months	>50% reduction
1	Gharib 1987	Double-blind RCT	N=53 T=28 (26) C=25 (22)	T=42±15 C=48.2±17	STN size≤3 cm	N/A	3 µg/kg/d	6	T=4 C=5
2	Reverter 1992	RCT with no placebo	N=40 T=20 (20) C=20 (20)	T=40.1±8.2 C=39.4±12.8	STN	<0.1	200 µg/d	12	T=4 C=3
3	Papini 1993	Single-blind (clinical evaluation) RCT	N=101 T=51 (46) C=50 (44)	T=43±10 C=42±11	STN cystic volume≤ 1 ml	0.05	2 µg/kg/d	12	T=10 C=3
4	La Rosa 1995	Single-blind (ultrasound examiner) RCT	N=45 T=23 (23) C=22 (22)	T=35.7±11.6 C=41±12.9	Solid STN cystic≤10%	<0.3	1.0 µg/kg/d	12	T=9 C=0
5	Papini 1998	RCT with no placebo	N=83 T=42 (37) C=41 (32)	T=41.4±12.5 C=41.9±12.7	Solid STN size 1-3 cm	0.05	2 µg/kg/d	60	T=20 C=9
6	Larijani 1999	Double-blind RCT	N=62 T=32 C=30	T=34.4±9.4 C=37.1±11.8	Solid STN	N/A	1.5-2µg/kg/d	12	T=6 C=4
7	Zelmanovitz 1998	Double-blind RCT	N=45 T=21 (19) C=24 (23)	T=44.8±10.3 C=41.3±13.1	STN cystic≤20%	<0.3	2.5-3µg/kg/d	12	T=6 C=2
8	Koc 2002	Crossover RCT	N=41 T=21 (19) C=19 (18)	N/A	STN cystic≤20%	N/A	1.5 µg/kg/d (low); 4 µg/kg/d (high)	12	T=8 C=4
9	Wémeau 2002	Double-blind RCT	N=123 T=64 (58) C=59 (52)	T=40±9.03 C=38.2±9.24	STN cystic≤20% nodule size<3 cm	<0.3	2.5 µg/kg/d	18	T=17 C=10
10	Larijani 2005	double-blind RCT	N=58 T=31 (25) C=27 (20)	T=34.4±9.4 C=37.1±11.8	STN	<0.1	1.5-2 µg/kg/d	24	T=6 C=3
11	Papini 2007	RCT with no placebo	N=41 T=21 (19) C=20 (18)	T=46.5±8.2 C=47.1±7.7	STN cystic≤20%, nodule size>3 cm volume>5 ml	<0.3	1.5 µg/kg/d	12	T=0 C=0
12	Bayani 2011	RCT with no placebo	N=41 T=20 (17) C=20 (17)	T=41.6±9.4 C=44.5±10.1	STN	<0.6	50 µg/d	6	T=1 C=3

RCT=randomized controlled trial; N=total participant; T=thyroid hormone suppressive therapy; C=placebo/no treatment, STN=solitary thyroid nodule; N/A=not applicable

We excluded the studies if the examiner did not use ultrasound to measure the thyroid nodule volume. We excluded the studies if the examiner did not use ultrasound to measure the thyroid nodule volume.

STUDY SELECTION AND DATA EXTRACTION

Four independent reviewers independently screened all titles and abstracts of the studies identified from searching strategies. Irrelevant and duplicate studies were excluded. We read the full text of all potentially relevant studies. The disagreement was resolved by discussion. We independently extracted the data. Any discrepancies were resolved by discussion.

QUALITY OF REPORTING AND RISK OF BIAS

The four authors evaluate the quality and risk of bias of the included study with domain base-evaluation following The Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. The domain base-evaluation evaluate in random sequence generation, allocation concealment, blinding or masking of the patient and health personnel, blinding of outcome assessment, missing outcome data, selective reporting, and others bias. They specify the criteria and classify the study into three group; low risk, high risk, and unclear risk. To assess the publication bias, we used a funnel plot of intervention effect estimates vs. the standard error for the studies presenting data for reduction of nodule volume.

DATA ANALYSIS

The effect of the estimate was pooled and calculated as risk ratio with 95% confidence intervals for dichotomous outcomes both benefit and adverse reaction. All analyses were performed with Revman 5.2 statistical software using fixed effect model. We explored both clinical heterogeneity and statistical heterogeneity using chi-square test of heterogeneity and the I^2 statistic to measure heterogeneity. Significant heterogeneity was considered if I^2 was more than 50%. To examine the effect of removing studies with the greatest potential for risk of bias, we conducted a sensitivity analysis regarding detection, attrition bias and the dose of levothyroxine.

RESULTS

Overall 3867 records identified through database searching and 8 records identified through hand searching. Of these, 2478 records after duplicates removed were identified. After screened titles and abstracts, 2456 records were excluded and 23 full-text articles were assessed for eligibility. Eleven were excluded, the reasons for exclusion were summarized in Figure 1. Twelve randomized controlled studies were eligible for meta-analysis, 9 studies comparing levothyroxine and placebo or no treatment. Two studies had additional treatment arms, one studies also compared with percutaneous laser ablation and another also compared with potassium iodide. However, these arms were not included for our analysis. One study was randomized crossover study, we included only the first phase of that trial to our meta-analyses. The included studies assigned 731 patients receiving either levothyroxine (n=374) or placebo/no treatment (n=357).

Figure 2. Risk of bias
Panel A, risk of bias graph and Panel B, risk of bias summary

STUDY CHARACTERISTICS

The included studies were conducted in Iran, Italy, Germany, France, Spain, Brazil, the United state of America and Turkey. Six studies were double-blind, one was cross-over trial, remaining study was not double-blind. Seven hundred and thirty-one participants were enrolled in the studies; their mean age from 32 to 48.2 years while one study did not provide the mean age of participants. The thyroid hormone doses used in eligible studies was 50 to 200 micrograms per day. The durations of eligible studies were varied from six months to five years, most of them had twelve months of follow-up duration (Table 1).

BIAS RISK ASSESSMENT

Twelve studies were assessed using domain base-evaluation. Only one study was judged to have the low risk of bias in all domain, seven studies were high risk in the domain of incomplete outcome data (Figure 2). Eleven of 12 studies had the unclear risk of bias in the domain of allocation concealment and random sequence generation.

REDUCTION OF THE NODULE VOLUME

The meta-analyses that included 2 studies which followed up for 6 months enrolled 93 participants showed no benefits of thyroid hormone suppressive treatment for the reduction of the

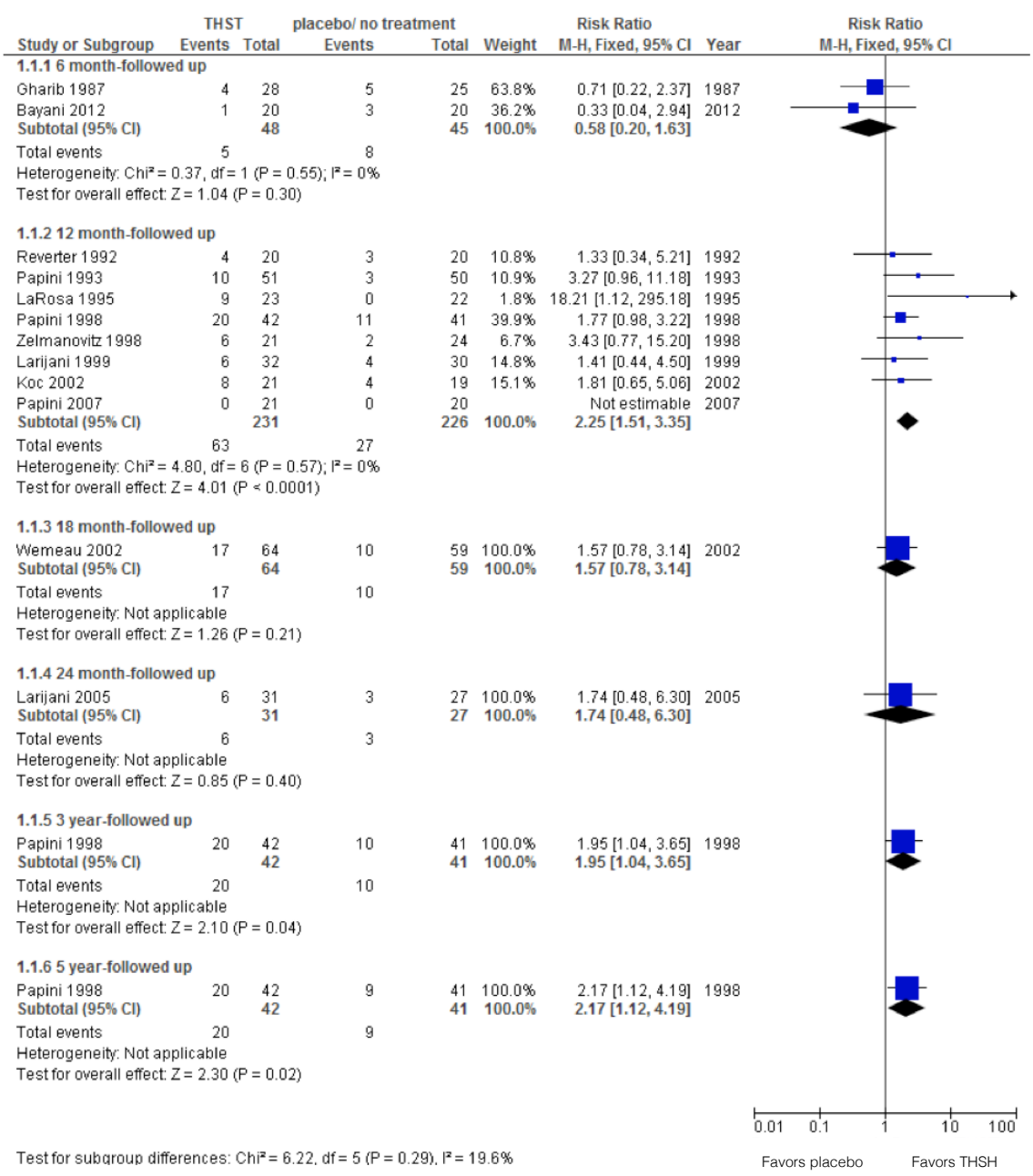

Figure 3. The forest plot showing meta-analyses of reduction of nodule volume >50% in thyroid hormone suppressive therapy comparing with placebo/no treatment for benign solitary thyroid nodule

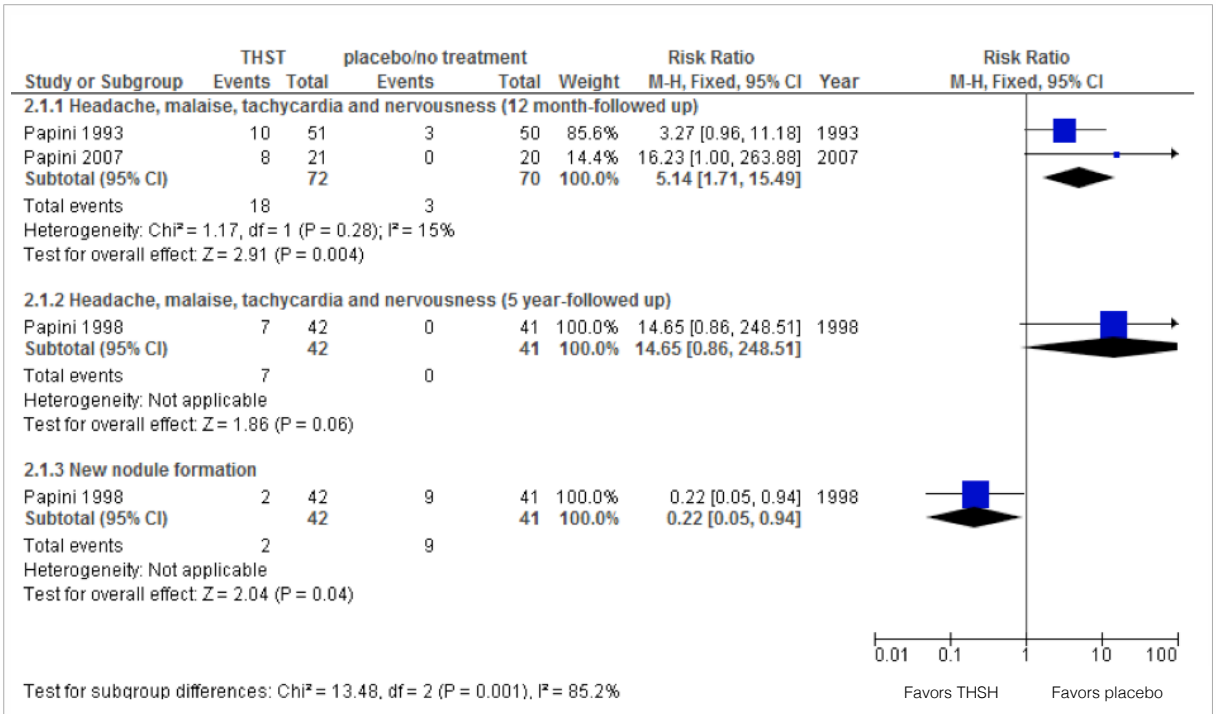

Figure 4. The forest plot showing meta-analyses of adverse reactions and nodule formation in thyroid hormone suppressive therapy comparing with placebo/no treatment for benign solitary thyroid nodule

nodule volume more than 50% from the baseline (10.4% in treatment group and 17.8% in control group; risk ratio=0.58; 95% CI [0.20 to 1.63]; chi-square=0.37; I^2=0%). However, the meta-analyses which included 457 participants from 8 studies that followed up for 12 months showed that thyroid hormone suppressive treatment had benefit significantly for reducing thyroid nodule volume more than 50% from the baseline (27.3% in treatment group and 11.9% in control group; risk ratio=2.25; 95% CI [1.51 to 3.35]; chi-square=4.80; I^2=0%). The meta-analyses of one study followed up for 18 months and one study followed up for 24 months, it found that thyroid hormone suppressive therapy had no benefits for reducing thyroid nodule more than 50% from the baseline (risk ratio=1.57; 95% CI [0.78 to 3.14] and risk ratio=1.74; 95% CI [0.48 to 6.30], respectively).

Nonetheless, one study that presented the results of the treatment at 3 years and 5 years, it found that the proportion of patients that had 50% reduction of thyroid nodule volume from the baseline was higher in the treatment group (47.6% and 47.6% at 3 and 5 years, respectively) than that of the control group (24.4% and 21.9% at 3 and 5 years, respectively) (risk ratio=1.95; 95% CI [1.04 to 3.65] and risk ratio=2.17; 95% CI [1.12 to 4.19] at 3 and 5 years, respectively) (Figure 3).

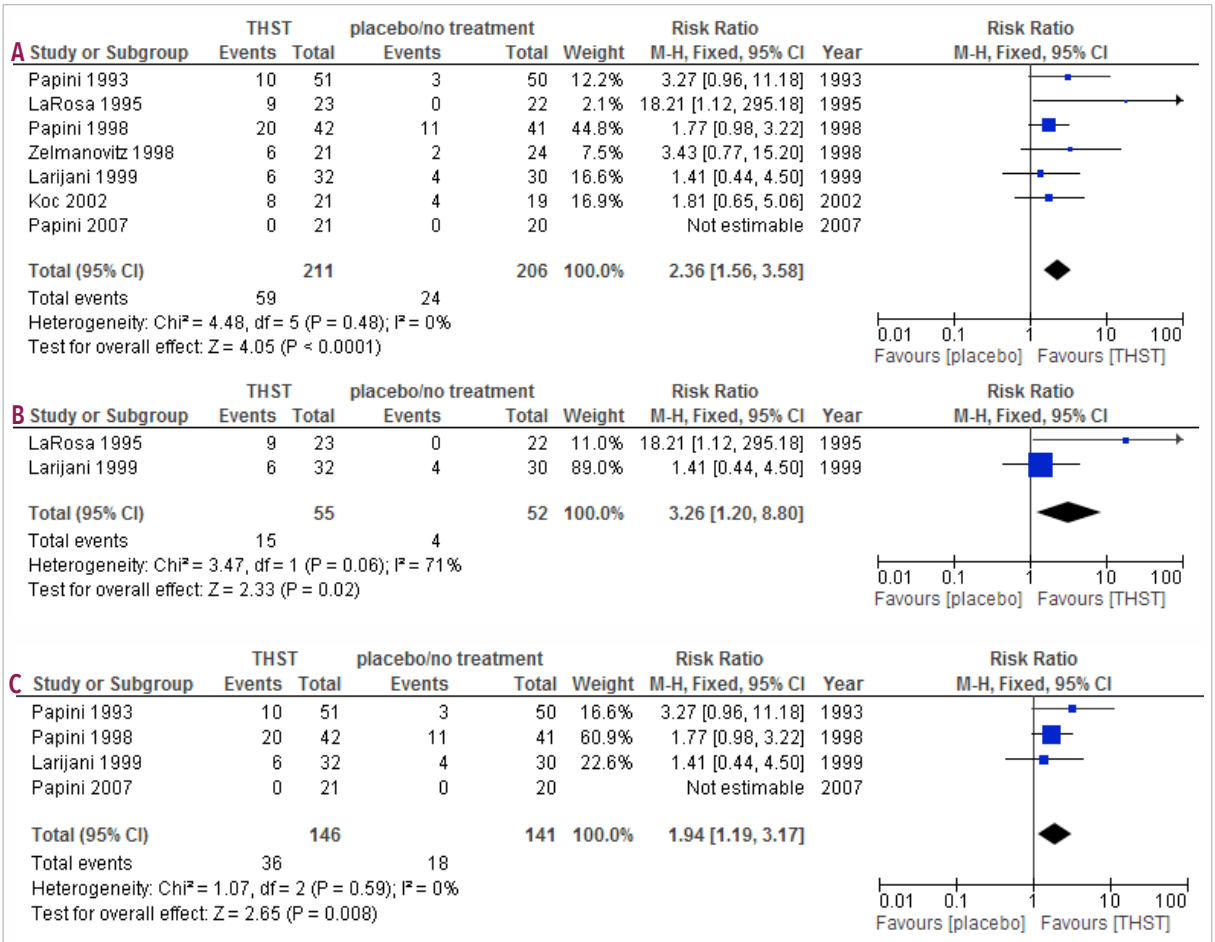

Figure 4. Sensitivity analysis showing meta-analysis of reduction of nodule volume >50% in thyroid hormone suppressive therapy comparing with placebo/no treatment for benign solitary thyroid nodule

Panel A, excluding high risk of bias study regarding blinding of ultrasonographic assessors; Panel B, excluding studies with attrition bias; Panel C, studies using 1.5-2 μg/kg/d of levothyroxine for treatment group

ADVERSE REACTION

Adverse reaction of thyroid hormone suppressive therapy were mentioned in three studies including headache, malaise, tachycardia and nervousness and they were found more often in the treatment group than the control group. Two studies were followed up for 12 months showed 25.0% of the patients in the treatment group and 4.3% in the control group experienced headache, malaise, tachycardia and nervousness (risk ratio=5.14; 95% CI [1.71 to 15.49]; chi-square=1.17; I^2=15%). One study followed up for 5 years showed only patients in treatment group (16.7%) experienced these reactions (risk

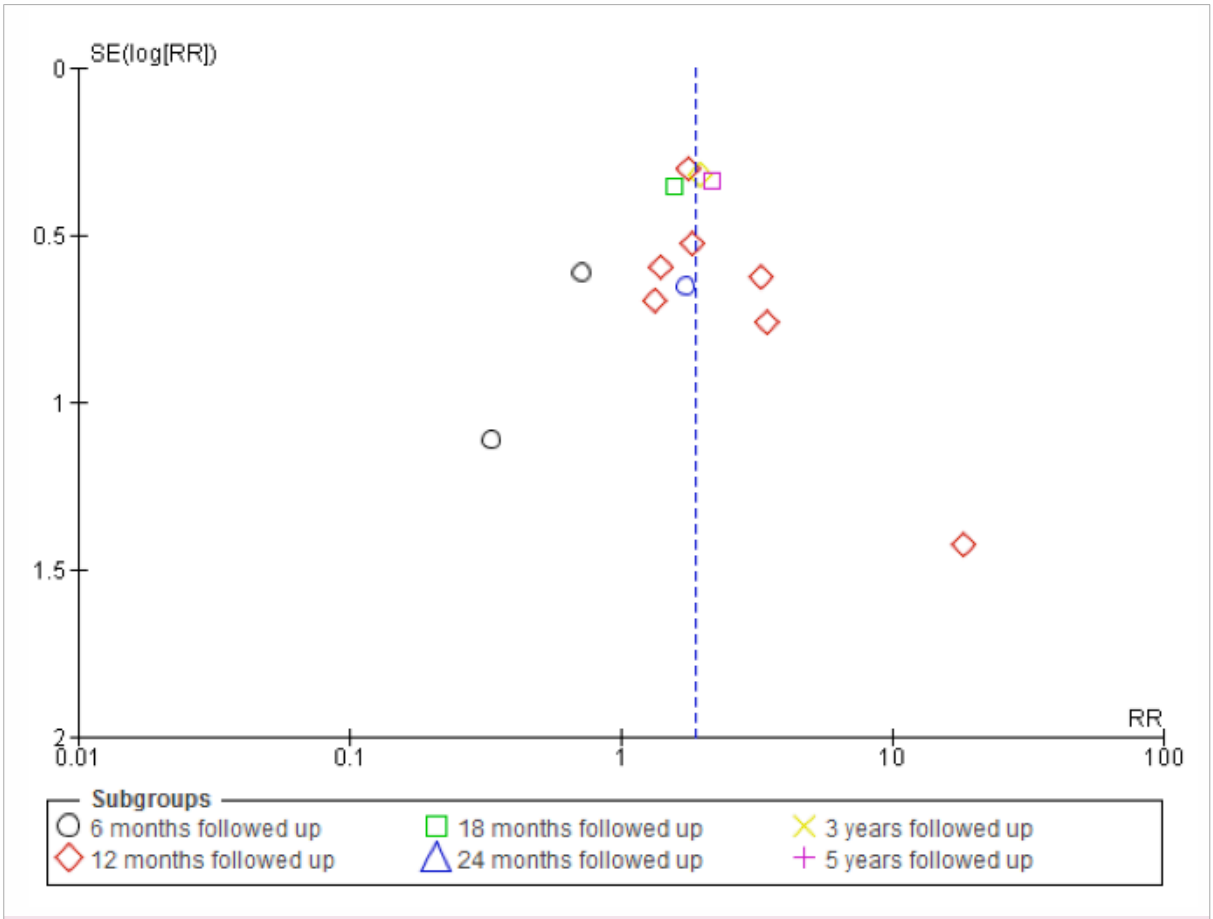

Figure 6. Funnel plot of studies included in the analyses

ratio=14.65; 95% CI [0.86 to 248.51]) (Figure 4, Panel A and B).

NEW NODULE FORMATION

Only one study presented the formation of new nodule during followed up for 5 years. Proportion of patients in control group developed new nodule more than treatment group, 9 of 41 in control group (21.9%) and 2 of 42 in treatment group (4.8%) (risk ratio=0.22; 95% CI [0.05 to 0.94]) (Figure 4, Panel C).

SENSITIVITY ANALYSES

We did the sensitivity analysis for 12-month followed up studies including 7 studies after excluding 1 study with high risk of bias according to the blinding of ultrasonographic assessors (n=417). It found that the thyroid hormone

suppressive therapy still had benefit for reducing nodule volume (risk ratio=2.36; 95% CI [1.56 to 3.58]; P<0.0001 and chi-square=4.48; I^2=0%) (Figure 4, Panel A). To assessed potential of attrition bias, there were 2 studies included in our meta-analyses showed thyroid hormone suppressive therapy had benefit for reducing nodule volume significantly (risk ratio=3.26; 95% CI [1.20 to 8.80]; P=0.02). Nonetheless, its heterogeneity increased (chi-square=3.47; I^2=71%) (Figure 4, Panel B). According to the dose of levothyroxine, we included 4 studies which used 1.5-2 μg/kg/d of levothyroxine for treatment group in our meta-analysis. That showed the thyroid hormone suppressive therapy also had benefit for reducing thyroid nodule volume (risk ratio=1.94; 95% CI [1.19 to 3.17]; P=0.008 and chi-square=1.07; I^2=0%) (Figure 4, Panel C).

PUBLICATION BIAS

We assessed the potential publication bias using a funnel plot which constructed from the 12 trials included in the analysis appeared to be symmetrical (Figure 6).

DISCUSSION

The main findings of our meta-analyses showed the thyroid hormone suppressive therapy had an effect on reducing nodule volume at 12-month, 3-year and 5-year followed up however it had no benefits for reducing nodule volume at 6, 18, 24 months followed up. Even though we excluded the studies with high risk of bias in 12-month followed up studies, the thyroid hormone suppressive therapy still showed benefits for reducing nodule volume. Patients who received thyroid hormone more experienced side effects including a headache, malaise, nervousness, and tachycardia than that of the control groups. We also found the lower proportion of patients with new thyroid nodule formation in the treatment group during followed up for 5 years.

STRENGTH AND LIMITATION OF THE REVIEW

Our systematic review followed the Cochrane Collaboration Handbook for intervention review version 5.1.0. We included the studies with no language restrictions. Four authors screened all titles and abstracts, extracted data independently. We included more new randomized controlled trial after the latest meta-analysis.[2,3,8] Thus the present review had higher study population. The present review also examined the risk of the bias of each study carefully using domain base-evaluation. It seemed that low-quality studies tended to have small effects on our findings. We also investigated the effects of the treatment regarding the duration of follow-up. Moreover, our meta-analyses had high homogeneity that confirmed the potential benefit of the treatment. One of the limitations of our review was the high risk of attrition bias of the included studies. Moreover, three studies with potential to be included in our review had to be excluded due to the inability to find full-text article and outcome in

term of thyroid volume reduction more than 50% from the baseline even the attempt to contact the authors of those studies. Thus, publication bias was unavoidable.

COMPARISON WITH OTHER STUDIES

Our main result which followed up for 12 months or longer for reducing nodule volume is unlikely with a previous meta-analyses that included 6 randomized controlled trials showed the thyroid hormone suppressive therapy had no significant benefit for reducing nodule volume more than 50% in patients with benign solitary thyroid nodule (risk ratio=1.9; 95% CI [0.95 to 3.81]).[2] However, our result for reducing nodule volume which followed up for 12 months or longer is similar to that of the recent meta-analyses. A more recent meta-analysis including 3 additional randomized controlled trials found that the thyroid hormone suppressive therapy had benefit for reducing nodule volume more than 50% from baseline significantly (risk ratio=1.88; 95% CI [1.18 to 3.01]).[3] The most recent meta-analyses that including 8 randomized controlled trials and 3 cohort studies, the results also confirmed that the thyroid hormone suppressive therapy had benefit for reducing nodule volume (risk ratio=1.68; 95% CI [1.3 to 2.1]).[8] Nonetheless, our meta-analyses included larger recent randomized controlled trials comparing with these previous studies. Moreover, our meta-analyses used subgroup analyses according to the duration of followed up thus it had higher homogeneity than those previous studies which did not use subgroup analyses. No previous systematic reviews reported the side effects or adverse events of thyroid hormone suppressive therapy. Our meta-analyses also showed side effects including headache, malaise, tachycardia, nervousness that were found higher in the treatment group.

CONCLUSION AND IMPLICATIONS

Thyroid hormone suppressive therapy shows the benefits for reducing the volume of benign solitary thyroid nodule at 12 months, however long term use of thyroid hormone leading to increased risk of side effects including a headache, nervousness, tachycardia, and malaise. Thus, the practitioner should consider risks and benefits of thyroid hormone suppressive therapy for the patients individually. Longer and larger cohort studies should consider more outcome of the adverse events of the suppressive therapy e.g., malignant transformation.

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"I shall either find a way or make one"

-Hannibal Barca

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