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Gynecological Morbidity among Women in Reproductive Age: A Systematic Review and Meta-Analysis

Merga Dheresa1*, Nega Assefa1, Yemane Berhane2, Alelmayhu Worku2, Bizatu Mingiste1 and Yadeta Dessie1

¹Department of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

*Corresponding author: Dheresa M, Department of Health and Medical Sciences, Haramaya University, Harar, Ethiopia, Tel: +251 92 592 0594; E-mail: mderesa@yahoo.com

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Abstract

Background: Prevention against infection and dysfunction of reproductive organ including sexually transmitted disease is one of the three dimensions of reproductive health. Gynecological morbidities affect women's physical health, sexual function, social role, psychological life and religious life. For accurate estimation of gynecological morbidity, population based data are considered to be gold standard. There are no global wide population studies on gynecological morbidities. In this paper, we aimed to determine the prevalence of gynecological morbidity among the reproductive age women in the world.

Methods: Using various key words, electronics databases were searched systematically to identify observational studies published so far in English. Meta-analysis was made to summarize the prevalence of gynecological morbidity. A random-effects model was used to calculate pooled prevalence. Publication bias was evaluated by testing for funnel plot asymmetry, Begg's rank correlation test and Egger's linear regression test. All statistical calculations were made using STATA Version 12.0 software.

Result: Eighteen studies, at least with one outcome variable were included in the final analysis. Ten studies were eligible for pelvic organ prolapse, 8 were eligible for infertility, 11 for menstrual disorder, and 15 for reproductive tract infection. The summarized random effect prevalence of pelvic organ prolapse was 13%, infertility was 8%, reproductive tract infection was 38%, and menstrual disorders were 28%. The overall pooled random effect prevalence of gynecological morbidity was 22% (95% CI=17%-27%, I2=99.38%, p=000). The potential publication bias was suggested by funnel plot asymmetry.

Conclusion: The polled prevalence of overall gynecological morbidity was high. This pooled prevalence enabled us to conclude that the effect of gynecological morbidities is high to hamper the productivity of reproductive age women in the world particularly in a developing nation.

Keywords: Gynecological morbidity; Systematic review; Meta-analysis; Women

Introduction

Maternal health has been given due attention since 1978 Alma-Ata declaration and it is considered as one component of the basic primary health care. Even though priority has been given to maternal mortality prevention, little attention is given to non-pregnant women [1].

However, in the 1994 International conference on Population and Development held in Cairo and in the 1995 World Congress on women which held in Beijing, general attention has been given to comprehensive women's health. This shifts orientation of fertility reduction and population policies to reproductive health [2]. Reproductive health is a state of complete physical, mental and social wellbeing; it is not merely the absence of disease or infirmity in all matters relating to the reproductive system and its functions and processes [3].

Protecting against infections and dysfunctions of the reproductive tract including sexually transmitted infections, avoiding of unwanted pregnancies, and keeping safe motherhood are the broad dimension of reproductive health among adult women [4].

Obstetrics, Gynecological, and Contraceptive morbidities are the three broad categories of reproductive morbidities [5]. Gynecological morbidity is structural and functional disorder of the reproductive tract (genital tract). Though gynecological morbidity is not related to pregnancy, delivery and puerperum, it may be related to sexual behavior [6,7].

Gynecological morbidities have negative impact on women health-related quality of life, in terms of marital disharmony excluding them from social and religious life [8]. The untreated conditions can cause pregnancy related complications, congenital infections, and chronic pain which significantly increase the risk of acquiring Pelvic Inflammatory Disease and HIV [9]. Gynecological disorders have a substantial impact on female reproductive ability, and mental health ability which perform routine physical activities [10].

Community based gynecological morbidity has served as important tool for epidemiological surveillance, health service planning, and policy advocacy; thus, it is considered to be the gold standard for research on gynecological morbidity among women [11,12]. There is a

²Addis Continental Institutes of Public Health, Addis Ababa, Ethiopia

paucity of population based research on gynecological morbidities with the prevalence ranges of 24.4% to 79.4% [4,13-15].

There are no global wide studies on the magnitude of gynecological morbidities that can be used for policy advocacy. Therefore, summarizing the prevalence of gynecological morbidity among reproductive age women is provided to develop research priorities. We performed a systematic review and meta-analysis on studies conducted on gynecological morbidities which aimed at exploring the prevalence of gynecological morbidities among reproductive age women in the world.

Methods

Literature search strategy

This systematic review was conducted based on PRISMA guidelines [16]. We searched all published articles on the prevalence of gynecological morbidity. Electronic data bases such as PubMed were searched to identify observational studies on the subject.

Papers were also identified by searching references from all included studies. No date restriction was applied in the search. The authors first screened the title, and abstracts. Then reviewed the full-text of the eligible articles.

Criteria for inclusion and exclusion

We included all epidemiologic studies which reported the prevalence of gynecological morbidity among 15-49 years old women all over the world. Only studies which used random sampling or census data to find participants were included.

All source studies were original cross-sectional study or a baseline survey of longitudinal study which is written in English and contained

the minimum information necessary to calculate pooled analysis of prevalence (number of the subjects and number of gynecological morbidity events).

Studies were included if they explicitly defined gynecological morbidity which in turn may include at least one types of gynecological morbidity (i.e. Reproductive tract infection, menstrual dysfunction, pelvic organ prolapse and infertility).

We excluded studies if the participants were not in the age range of 15-49, pregnant women, if the study reported only the overall prevalence of gynecological morbidity without mentioning the morbidity types. We also excluded studies not only with qualitative study but also studies that utilized non-random sampling.

Data extraction

The standardized data abstraction form was designed to capture and code all relevant studies level information required for analysis. Authors selected the studies and extracted the data. For all included studies, we recorded the following information:

- Author
- Year of publication
- Countries
- · Sampling method
- · Data collection method
- Number of subjects
- Number of people with gynecological morbidity

Quality assessment of included studies

We used the Joanna Briggs Institute (JBI) Prevalence Critical Appraisal Tool [17] to assess quality of individual paper (Table 1).

JBI Quality Items												
S. No	Author (year)	1	2	3	4	5	6	7	8	9	10	Score
1	Abraham A et al. (2014)	Y	Y	Υ	Y	Y	Y	Y	Y	Y	Υ	10
2	Verma A et al. (2015)	Y	Y	Υ	Υ	Υ	N	U	Y	Y	N	7
3	Fahimeh et al. (2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
4	Filippi V et al. (1997)	Y	Y	Y	N	Y	Y	Y	Y	Y	Υ	9
5	Inamdar IF et al. (2013)	Y	Y	Υ	Y	Y	Y	N	Y	Y	Υ	9
6	Masterson A et al.(2014)	Y	Y	Υ	Y	Y	U	U	Y	Y	Υ	8
7	Gokler M et al. (2014)	Y	Y	Υ	Υ	N	Y	Y	Y	Υ	Υ	9
8	Miteshkumar N (2010)	Y	Y	Υ	Υ	Υ	Y	Y	Y	Y	Υ	10
9	Bhatnagar N et al. (2013)	Y	Y	Υ	Y	Y	U	U	Y	Υ	Υ	8
10	Philippov O et al. (1998)	Y	Υ	Υ	Y	N	Y	Y	U	N	N	6
11	Chellan R (2004)	N	N	N	N	N	N	N	N	N	N	10
12	Riyami et al. (2004)	Y	Y	Υ	Υ	Υ	Y	Υ	Y	Y	Υ	10
13	Garg S et al. (2002)	U	Υ	U	Y	Y	Y	U	Υ	N	N	5
14	Poornima S et al. (2013)	Y	Y	Υ	Υ	Υ	Υ	Υ	N	N	Υ	8

15	Kaur S et al. (2013)	Υ	N	U	N	Y	Υ	Y	Υ	Y	Υ	7
16	Kumari S et al. (2000)	Υ	U	U	N	Y	Y	Υ	Y	Y	N	6
17	Siae M et al. (2002)	Υ	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
18	Gosalia VV et al. (2012)	Υ	Υ	Υ	Y	Υ	N	N	N	N	N	5

Table 1: Quality assessment of the 18 paper used for the meta-analysis [Y= yes, N=No, U=unclear].

Statistical analysis

To include proportion close to 0 and 1, we enabled the Freeman-Tukey double arcsine transformation option (ftt) [18]; otherwise, studies with estimated proportion at 1 and 0 would be excluded from the analysis leading to a biased pooled estimate. The transformed prevalence is weighted very slightly towards 50% and, thus, studies with prevalence of 0 can be included in the analysis [19].

Meta-analyses were conducted using the metaprop [18] command for prevalence and metainf for influence of single study. Meta-analyses were conducted summarizing the prevalence of gynecological morbidity among women of reproductive age. First, the prevalence of each type of gynecological morbidity (pelvic organ prolapse, infertility, reproductive tract infection and menstrual disorder) was analyzed separately.

Then overall gynecological morbidity prevalence was assessed by stratifying by types of gynecological morbidities. According to the expected heterogeneity across studies, a random-effects model was used to calculate pooled prevalence. In all cases 95% confidence intervals were calculated using the binomial exact method to calculate. Statistical heterogeneity was evaluated with the Cochran chi-square (χ^2) and quantified with the I2 statistic (low is 25%, moderate 25-50%, high 50%) [20,21].

Publication bias was evaluated by testing for funnel plot asymmetry, Begg's rank correlation test and Egger's linear regression test. Significance was set at a P value of less than 0.05. Sensitivity analyses include investigation of the influence of a single study on the combined association by omitting one study in the pooled analysis. All statistical calculations were made using the Stata Statistical Software Package, Version 12.0. Ancillary analyses were performed using comprehensive meta-analysis software.

Result

Systematic review

The literature search returned 222 publications from Medline/PMC. Additional 60 studies were included from other sources (Google Scholar and reference lists of relevant publications).

Two hundred forty-two studies were remained after removing duplicates. While screening relevant titles, 102 studies were excluded. This means a total of 140 full texts were assessed. The outcome variable for this study was gynecological morbidity (reproductive tract infection, menstrual disorder, pelvic organ prolapse and infertility).

Studies which report at least one types of the gynecological morbidity were accepted for meta-analysis. After applying the quality criteria, 122 studies were further excluded (some of the studies were systematic review, several were studied among women out of reproductive age, and others were qualitative study which did not provide numerical estimates on incidence and/or prevalence of gynecological morbidity.

Still other studies were not mentioned which types of gynecological morbidity they studied). Finally, 18 studies were retained for the review and meta-analysis (Figure 1).

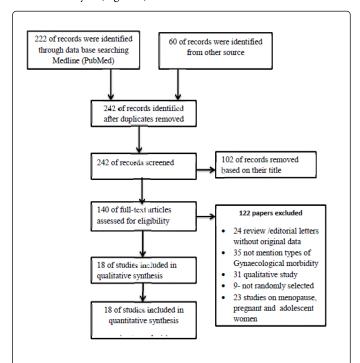


Figure 1: The Flow diagram of inclusion and exclusion identified was studied for the meta-analysis of overall prevalence.

Study characteristics

The retained 18 studies [10,13,15,22-36] were conducted in different parts of the globe. Almost 33.3% of studies were conducted in urban area [15,24,26,30,33,36], 11% were conducted in both urban and rural areas [27,31].

In addition, 5.5% in rural area and the rest, places where studies are conducted is not mentioned as urban or rural areas (Table 2).

					Publication bias	
Categories	Q (heterogeneity statistics)	*df	*I ² (Heterogeneity test)	р	P (Begg's test)	P (Egger's test)
*POP	1123.11	9	99.20%	<0.001	0.283	0.004
Infertility	353.79	7	98.02%	<0.001	0.266	0.038
*RTI	1360.3	14	98.97%	<0.001	0.138	0.4
Menstrual disorder	537.72	10	98.14%	<0.001	0.533	0.142
Overall	6975.99	43	99.38%	<0.001	0.56	0.235
B/n sub group	47.37	3	-	<0.001	-	-

Table 2: Heterogeneity and publication bias test in four types and overall gynecological morbidities among reproductive age women [*I² = the variation in ES attributable to heterogeneity, *df = degree of freedom, *POP = pelvic organ prolapse; *RTI=reproductive organ prolapse].

From the retained 18 studies, 2 papers contain two outcome variable (one study reports menstrual disorder and reproductive organ prolapse while the other reports reproductive tract infection and pelvic organ prolapse) [23,31]. Six studies contain three outcome variables (4 of them contain menstrual disorder, reproductive organ prolapse and reproductive tract infection. The rest 2 studies report menstrual disorder, reproductive tract infection and infertility) [10,15, 25,30,33,35,36]. Four studies contain four outcome variables (menstrual disorder, pelvic organ prolapse, reproductive tract infection and infertility) [13,22,26,32].

Six papers reported only one outcome variables (3 of them report only reproductive infection, 2 of them report infertility and the rest 1 report pelvic organ prolapse) [24,27-30,34] (Table 2). Ten studies were eligible for pelvic organ prolapse [10,13,15,22,26,29,31,32,35,36] and

contain 8,703 sample size. The prevalence of the pelvic organ prolapse ranges from 0.4%-41%. Eight studies were eligible for infertility [13,22,25,26,28,30,32,33] and contain 6,436 sample size. The prevalence of infertility among the paper was ranging from 1%-16%.

For menstrual disorder, 11 studies were identified [10,13,15,22,23,25,26,32,33,35,36], the total sample population were 7,247 and prevalence of menstrual disorder was ranging from 11%-53%. Among the identified paper, 15 studies were eligible for reproductive tract infection [10,13,15,22-27,31-37] and contain 26,248 sample sizes.

The prevalence of reproductive tract infection ranges from 7-70%. The sample size of individual studies ranged from 200-18,040 (Table 3).

					Outcome Variable			
S. No	Author (year)	Country	Age	Sample size	Menstrual disorder	RTI*	POP*	Infertility
1	Abraham A et al. (2014)	India	15-45	540	135	39	2	17
2	Verma A et al. (2015)	India	15-44	215	-	91	-	-
3	Fahimeh et al. (2011)	Iran	18-45	1117	336	420	462	-
4	Filippi V et al. (1997)	Turkey	15-49	862	103	345	147	-
5	Inamdar IF et al. (2013)	India	15-49	750	351	189	114	87
6	Masterson A et al. (2014)	Lebanon	18-45	452	242	241	-	-
7	Gokler M et al. (2014)	Turkey	18-49	570	-	-	-	73
8	Miteshkumar N (2010)	India	15-49	1046	403	587	-	12
9	Bhatnagar N et al. (2013)	India	15-49	750	115	82	27	26
10	Philippov O et al. (1998)	Siberia	18-45	2000	-	-	-	333
11	Chellan R (2004)	India	15-44	18040	-	5827	-	-
12	Riyami et al. (2004)	Oman	15-49	364	-	81	64	-
13	Garg S et al. (2002)	India	15-45	380	98	216	60	31
14	Poornima S et al. (2013)	India	15-49	400	83	282	-	27

15	Kaur S et al. (2013)	India	15-49	200	36	49	16	-
16	Kumari S et al. (2000)	India	15-49	2990	-	-	227	-
17	Siae M et al. (2002)	Tanzania	15-49	382	-	244	-	-
18	Gosalia VV et al. (2012)	India	15-49	750	195	198	3	-

Table 3: Summary of overall characteristics of studies retained for systemic review and meta-analysis [*pop=pelvic organ prolapse, *RTI=Reproductive Tract Infection].

Age of study participant was between 15-49 years. 51% of them were in the age ranges of 35-49 years. Regarding their marital status, 86.5% of women were currently married and 5% were never married. Among those currently married women 33% of them were married before the reach 18 years old. 87% of study participants were multiparous; 39% of the study participants were illiterate, 17.5% were attended primary education, and 43% were attended secondary education and above [10,13,15,22-36].

Pooled analysis in different outcome categories

Pelvic organ prolapse: The point prevalence of pelvic organ prolapse with 10 individual study populations ranges between 0% and 41%, with an overall summarized random effect meta-analysis prevalence of 13% (95% CI=8- 12, 12=99.31% p=0.000) (Figure 2).

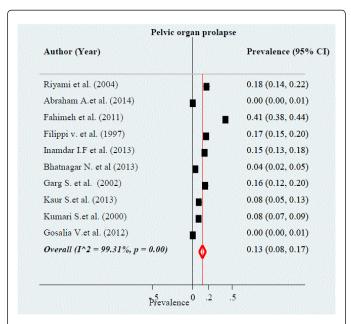


Figure 2: Random model meta-analysis of prevalence of pelvic organ prolapses among women.

Infertility: The prevalence point of infertility with 8 individual study populations ranged between 1% and 17%. The pooled meta-analysis prevalence of infertility was 8% (95%=4-12, I2=98.26%, p=000) (Figure 3).

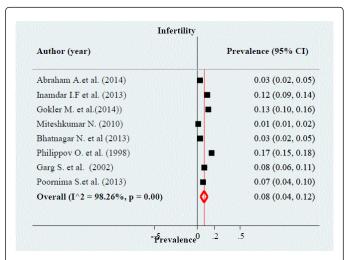


Figure 3: Random model Meta-Analysis of prevalence of infertility among women.

Reproductive tract infection: The prevalence point of reproductive tract infections among 15 individual studies ranged from 7% to 70% and an overall pooled meta-analysis prevalence was 38% (95% CI=30%-46%, I2=99.23%) (Figure 4).

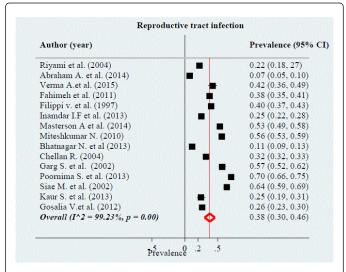


Figure 4: Random effect model meta-analysis of prevalence of RTI among women.

Menstrual disorder: Menstrual disorders' point prevalence ranged from 12% to 54% with 11 individual study population and the pooled

meta-analysis prevalence of 28% (95% CI=30%-46%, I2=98.30%) (Figure 5).

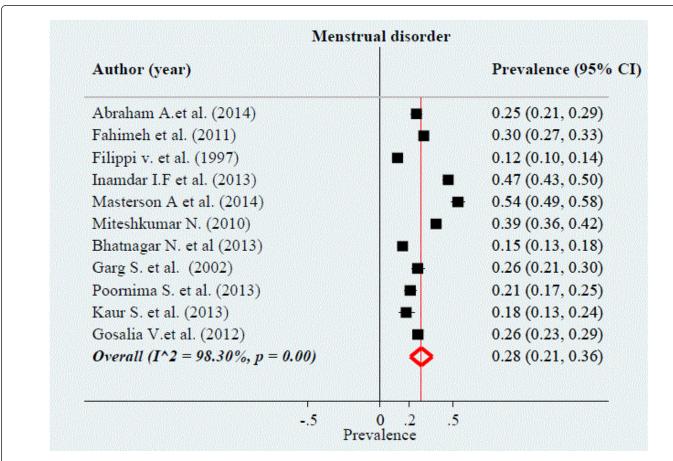


Figure 5: Random effect model meta-analysis of prevalence of menstrual disorder among women.

High level of heterogeneity (I2=98.30%-99.31%) was noted within the studies in each type of gynecological morbidities (Figures 2-5).

Overall gynecological morbidity prevalence

Overall gynecological morbidity prevalence was assessed all types of gynecological morbidities by stratifying. Pelvic organ prolapse with 11 studies, infertility with 8 studies, reproductive tract infection with 15 studies, menstrual disorder with 11 studies, totally 44(some individual studies have more than one outcome variable) studies with 48,634 study population were included in the overall pooled summary of meta-analysis prevalence.

The point prevalence of gynecological morbidity with 44 individual study populations ranges from 0% (in pelvic organ prolapse) to 70% (in reproductive tract infection).

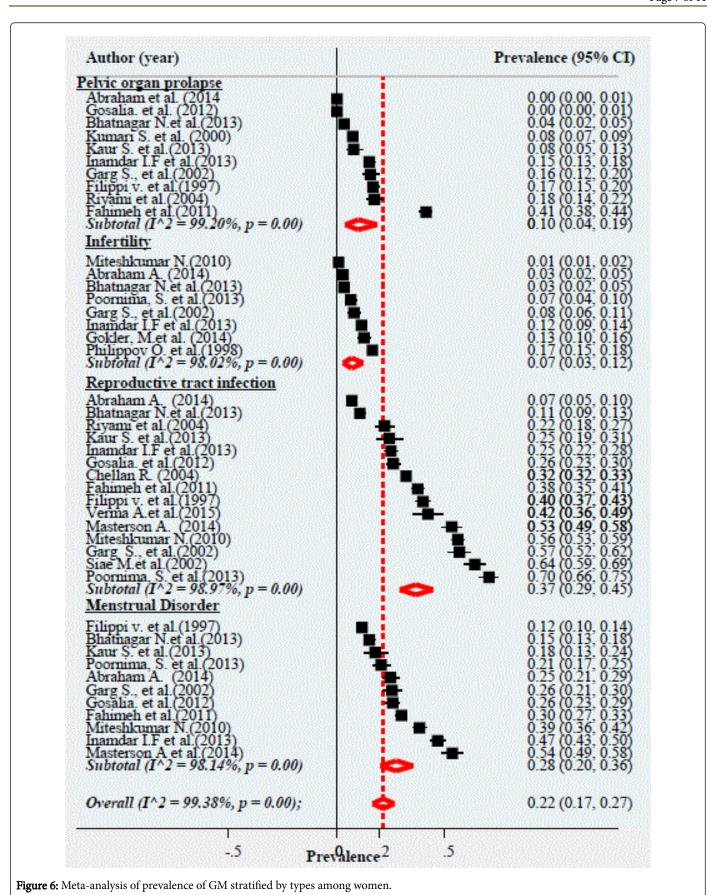
The overall pooled random effect meta-analysis prevalence of gynecological morbidity was 22% (95% CI=17%-27%, I2=99.38%, p=000) (Figure 6).

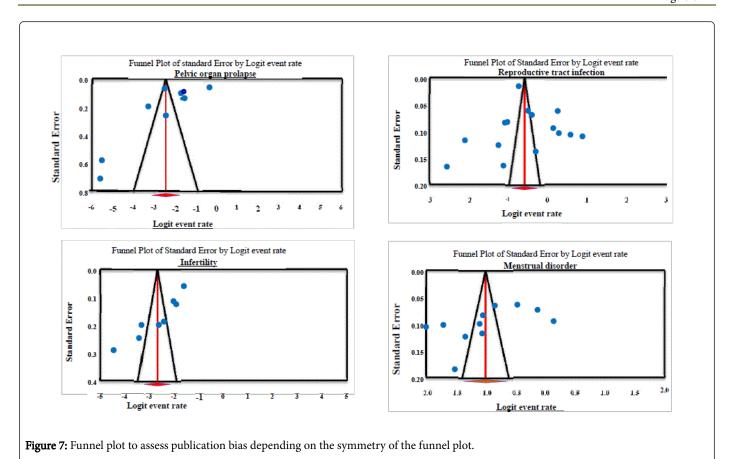
High level heterogeneity was noted within the studies and among groups of studies (I2=98.02%-99.20%, p=00) (Table 2).

Publication Bias

Publication bias was evaluated by testing for funnel plot asymmetry, Begg's rank correlation test and Egger's linear regression test. Egger's regression test indicated evidence of publication bias for gynecological morbidity (p=0.004 for pelvic organ prolapse and p=0.03 for infertility). However, there was no evidence of publication bias for reproductive tract infection (p=0.40), menstrual disorder (p=14) and overall gynecological morbidity (p=23).

Begg's test indicated that there was no evidence of publication bias of all types of gynecological morbidities (Table 2). Each funnel plot appears asymmetry that suggested the presence of a potential publication bias of all types of gynecological morbidities (Figures 7 and 8).





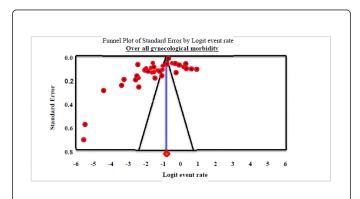


Figure 8: Funnel plot to assess publication bias using asymmetry of the plot.

Sensitivity analysis

To test the robustness of meta-analysis results, we performed graph of individual studies influence on the pooled meta-analysis prevalence using STATA command option (matainf). The pooled meta-analysis was influenced only by original study (Chellan R), so omissions of other studies make little or no difference. When (Chellan R) excluded from the pooled analysis, pooled prevalence of gynecological morbidity reduced from 22% (95% CI=17-27) to 21% (95% CI=16-27) but statistically not significant.

Discussion

This is a comprehensive report attempting to sensitize the prevalence estimation of gynecological morbidity among reproductive age women by using meta-analysis. This comprehensive systematic review with meta-analysis of observational studies conducted in the world included 18 reports and 31,808 women population. Thus, it was possible to provide a reliable estimate of prevalence.

Our comprehensive systematic review and meta-analysis found that 10% of women have had pelvic organ prolapse, 7% of them were infertile; reproductive tract infection is the most 37% followed by menstrual disorder 28%. The pooled random model meta-analysis of overall gynecological morbidity is 22% (95% CI=17%-27%). The average number of complaints of gynecological morbidity ranges from (1.2-1.5); different types of gynecological morbidities may appear concurrently on individual women. The existence of some types may favor condition for the occurrence of the other [13,38,39].

The studies included in this analysis were conducted among reproductive age women at house hold level and health facility among women seeking care for other than gynecological problem. All the studies were observational epidemiological cross-sectional studies drawing sample population by random sampling method.

The response of clients on gynecological morbidity varies by place where interview is conducted and the profession of the interviewer. Respondents complained many types of problem when they were interviewed in a health facility and by health workers [4,13,35]. The proportion of women reporting symptoms were the higher when they

were interviewed by physician at health facility than when they were interviewed by lay person at household level [35]. This result strongly suggests that anticipation of treatment influences responses, either by overcoming silence or inviting exaggeration [40]. The result of the prospective study also suggests that repeated interview may elicit greater reporting symptoms than a single interview. Such a trend may reflect the development of closer rapport between respondent and interviewer over successive round or improved proficiency on the part of interviews. Therefore, the results of cross-sectional studies did not compared with prospective studies [40].

Addressing gynecological morbidity is a complex process as women either don't consider it as a significant health problem or hesitate to talk on it. Even though, women with gynecological morbidity face serious social consequences in terms of marital disharmony, exclusion from social and religious life [41]. Gynecological morbidity has a great impact on life of women, their child and family as well. Women with gynecological morbidity may be challenged with multifaceted health, psychological and social problem. According to WHO, reproductive ill health accounts for 36.6% of the total disease burden among women aged 15 to 45 years at a global level [13]. It result in 250 million years of reproductive life loss each year in worldwide and reduce the overall productivity of women as much as 20% [36].

Majority of women do not seek health care until it becomes an emergency. Women were associated with causes of this morbidity with curse, evil eye, watch craft, excessive body heat, and sterilization. Some women accept the problem as normal health ill of women; as a result, they do not seek care [42,43]. Certain untreated conditions can cause pregnancy related complications, congenital infections, infertility, chronic pain and significantly increase the risk of acquiring Pelvic Inflammatory Disease and HIV [41].

Gynecological morbidity was associated with illiteracy, ignorance, gender discrimination and poor social status, lack of decision making power and inability to afford seeking health care, parity, early mirage and age [13,27,44-47].

Cultural sensitive prevention, care and treatment are needed to alleviate the burden of this problem. Educating and empowering women are the magic bullet to maximize women's health and quality of life. In turn, healthy women contribute a lot for countries development.

High levels heterogeneity exhibited within the studies and among groups of studies the (I2=98.02%-99.20%, p=00). Egger's regression test indicated evidence of publication bias for gynecological morbidity (p=0.004 for pelvic organ prolapse and p=0.03 for infertility). But, there was no evidence of publication bias for reproductive tract infection (p=0.40), menstrual disorder (p=14) and overall gynecological morbidity (p=23). Begg's test indicated no evidence of publication bias of all types of gynecological morbidities.

Studies included in this analysis were conducted in different setup, geographic location, among participants of different cultural background and economic difference with different methodology. This variation leads to heterogeneity of the studies. In addition to this, the bias may be introduced into each study. Some of the paper asked whether participants have problem at any time in the life, in the past 6 month, in the past 3 month and other asked whether they are currently experiencing it. Recall periods of more than 2-4 weeks for closed question, or few days for open-ended questions, they appear to introduce bias from under reporting and misclassification [11].

Measurement and definition variation also affect the results of the same studies. This problem is more observed on menstrual disorder variable. The common recorded types of menstrual disorder include volume (heavy, normal or light), regularity (irregular, regular or absent), frequency (frequent, normal or infrequent), and duration (prolonged, normal or shortened) of menstrual episodes. Each term could be interpreted differently across the globe. To avoid this confusion, the Federation of International Gynecological and Obstetrics (FIGO) introduced a new classification called the PALM-COEIN system of abnormal uterine bleeding (AUB). The basic system comprises four categories that are defined by visually objective structural criteria (PALM: Polyp, Adenomyosis, Leiomyoma, and Malignancy or Hyperplasia); five (COEIN: Coagulopathy, Ovulatory disorders, Endometrium, iatrogenic and not yet classified) [48,49].

The pooled meta-analysis was influenced only by original study (Chellan R) [27]. When (Chellan R) [27] excluded from the pooled analysis, pooled prevalence of gynecological morbidity reduced from 22% (95% CI=17-27) to 21% (95% CI=16-27) but statistically it is not significant. In our study, the individual studies did not influence the pooled estimated prevalence of gynecological morbidities.

Limitation

This systematic review is not free of limitation: majority of the papers used in this analysis were studied in South East Asia. The prevalence of gynecological morbidity from this analysis couldn't be inferred to other developing countries. Unpublished data did not include in this analysis and thus publication biased likely may occur. The other limitation was the papers included in this study were only papers that were written in English language. This may also introduce language bias.

Conclusion

The polled prevalence of overall gynecological morbidity was 22%. This prevalence is not an over estimated prevalence instead it may be underestimated because of silence of women in reporting the problem due to cultural influences, ignorance and embarrassment to talk about the problem. This study showed tips of the ice-berg of gynecological morbidities, and the magnitude of the problem is more than the reported one. From this prevalence, we can conclude that the effect of gynecological morbidity is high to hamper the productivity of reproductive age of women in the world particularly in developing regions.

The common reported gynecological morbidities were reproductive tract infection and menstrual disorders. Theses might be more prevalent among reproductive age women than other. Pelvic organ prolapse is common among menopause women than reproductive age women. Heterogeneity was noted in this analysis for the studies were drawn all over the world with different back ground and methodology. The burden of gynecological morbidity was higher among economically and culturally disadvantageous women.

Authors' Contributions

MD, NA, YB, AW, BM and YD, conceived and designed the paper, performed the statistical analysis, and wrote the paper. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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