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# Association of Helicobacter pylori Infections and Hyperemesis Gravidarum Women: A Case Control Study in Selected Healthcare Facilities in Addis Ababa, Ethiopia

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## Abstract

**Background:** Nausea and vomiting is a common and unpleasant problem in 75% to 80% of pregnancies. In some women nausea and vomiting is very severe and does not respond to simple diet manipulation and antiemetic agents. Hyperemesis gravidarum is one of the many problems during pregnancy; its etiology has not been clearly understood. But, infection with *Helicobacter pylori* have been considered as a risk factor in recent studies. However, complementary data is very limited in the Ethiopian context and this study sought to elucidate the possible association of *Helicobacter pylori* infection and hyperemesis gravidarum women attended in selected healthcare facilities in Addis Ababa, Ethiopia.

**Methods:** A case control study was conducted from July to October 2016 in Gandhi Memorial Hospital, and Kirkos and Kazanchis health centers in Addis Ababa among cases of 50 hyperemesis gravidarum women and controls of 100 women without hyperemesis gravidarum. A structured questionnaire was used to collect sociodemographic data. Venous blood samples were collected for hemoglobin concentration determination and stool samples were collected for the presence of *Helicobacter pylori* infection using stool antigens test kit and intestinal parasites by direct stool examination using wet smear and Formol-Ether concentration techniques. Urine analysis was done for ketone bodies. Data was summarized in frequencies and mean ± SD. Chi-square tests, Student "t" test and multivariate analysis were used. P-value < 0.05 were considered as statistically significant.

**Results**: The overall prevalence of *Helicobacter pylori* infection among pregnant women was 24.7% [37/150]. The prevalence of *Helicobacter pylori* infection was higher in pregnant women with hyperemesis gravidarum than pregnant women without hyperemesis gravidarum, 56% [28/50] and 9% [9/100] respectively, [$X^2$ = 39.626 P value = 0.000]. In this study there was a statistically significant association between *Helicobacter pylori* infection and low hemoglobin value, [OR = 4.121, 95% CI = 1.233 - 13.771, p = 0.024].

**Conclusion**: This study suggested that there was a strong association between *Helicobacter pylori* infection and hyperemesis gravidarum women. *Helicobacter pylori* could be considered as one of the risk factors for hyperemesis gravidarum. *Helicobacter pylori* infection was associated with low hemoglobin value. *Helicobacter pylori* infected hyperemesis gravidarum pregnant women showed higher rates of anemia than pregnant women without Hyperemesis gravidarum. Further primary care level studies recommended to further explore whether screening *Helicobacter pylori* infection during pregnancy could benefit the mother and the fetus.

***Keywords:*** *Anemia; H. pylori; Pregnancy; Hyperemesis Gravidarum; Ethiopia*

## Abbreviations

Ab: Antibody; Ag: Antigen; ANC: Antenatal Care; ELISA: Enzyme Linked Immunosorbent Assay; EQA: External Quality Assurance; FGR: Fetal Growth Restriction; GI: Gastrointestinal; Hb: Hemoglobin; HCl: Hydrochloric Acid; HG: Hyperemesis Gravidarum; *H. pylori*: *Helicobacter pylori*; HpSA: *Helicobacter pylori* Stool Antigen Test; IDA: Iron Deficiency Anemia; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IQC: Internal Quality Control; SOP: Standard Operational Procedures; WHO: World Health Organization

## Introduction

*Helicobacter pylori* (*H. pylori*) infection in pregnancy is not only associated with gastrointestinal disorders such as hyperemesis gravidarum (HG), but also with iron deficiency anemia, fetal malformations, miscarriage, preeclampsia and fetal growth restriction [1,2]. These pregnancy associated disorders are potentially life threatening for both the mother and fetus or neonate [1,3].

Nausea and vomiting are a common and unpleasant problem in about 80% of pregnancies. In some women nausea and vomiting is very severe and does not respond to simple diet manipulation and antiemetic agents [4,5]. Although, pregnancy itself may increase the susceptibility to *H. pylori* infection, studies suggest that a significantly increased incidence of pregnant women with high *H. pylori* compared to women without pregnancy. Nonetheless, chronic infection with *H. pylori* has been reported to have a role in producing HG [3,6,7].

Estimates of severe nausea and vomiting of pregnancy vary greatly and range from 0.3% in a Swedish registry to as high as 10.8% in a Chinese registry of pregnant women. In U.S. alone, 59,000 pregnant women hospitalized annually due to severe nausea and vomiting of pregnancy [8]. The prevalence of severe nausea and vomiting of pregnancy in Ethiopia was reported in recent studies in different settings with 8.2% in Arba Minch area [9] and 74.5% in Addis Ababa, with 4.4% being demanded admission for severe conditions [10].

*H. pylori* infects as many as 50% of adults in the industrialized countries and 90% of adults in the developing world [11,12]. *H. pylori* colonizes and grows in human gastric epithelial tissue and mucus. Its presence is associated with gastritis and there is substantial evidence that it causes peptic and duodenal ulcers and chronic gastritis [13]. Once acquired, *H. pylori* infection usually persists for life unless treated by antimicrobial therapy. Since 1994, *H. pylori* has been classified as carcinogenic to humans [14]. The prevalence of *H. pylori* infection in pregnant women varies according to socioeconomic and demographic conditions, geographic area, and even the method used to test *H. pylori* infection [15]. The possible transmission route seems to be oral-oral, faecal-oral, and iatrogenic transmission and vectorial spread [16]. However, recent studies showed that mother to child transmission of *H. pylori* does not appear to occur during pregnancy or delivery [17].

*H. pylori* is a gram negative, spiral shaped and microaerophilic bacteria. *H. pylori* pathogenicity depends on several strain specific factors which includes specific genes conferring proinflammatory, cytotoxic and vacuolating properties. However. virulence factors such as urease and flagella are present in all strains and are critical for pathogenesis and colonization [18].

Currently, two categories of tests are available for the diagnosis of *H. pylori* infection. The invasive one which includes endoscopy with biopsy for histology, culture, and rapid urease test are not suitable for pregnant women. Another invasive test, the serological tests do not discriminate between current and past infections due to immunological scars resulted from previous infection and cannot reveal an ongoing infection [19,20]. The noninvasive urea breath test (UBT) which is considered as a gold standard could not be easily available due to logistic reasons. However, the noninvasive stool antigen test offers a simple, and yet robust alternative tests useful both in diagnosis and during follow up after eradication treatment. Moreover, the stool antigen test is cheaper than UBT with similar sensitivity and specificity [21]. So far, sufficient data was lacking that investigated the prevalence of *H. pylori* infection among hyperemesis gravidarum women in Ethiopian settings using available diagnostics. Therefore, this study was initiated to elucidate the possible association between *H. pylori* infection and hyperemesis gravidarum women who attended in selected healthcare facilities in Addis Ababa, Ethiopia.

## Materials and Methods

### Study design and study period

A case control study was conducted from July to October 2016 in Kirkos sub city at Gandhi memorial Hospital, and Kirkos and Kazanchis health centre in Addis Ababa, Ethiopia. Kirkos sub city has 11 districts with the size of 16.26 $km^2$ and an estimated population density of 13,501 people per $km^2$. The total projected population of Kirkos sub city is estimated to be 220,991 which is 8.07% of the entire population of Addis Ababa city administration (2007 CSA Censes), of which 103,334 (46.5%) are males and 117,677 (53.25%) are females. Women of childbearing age group constitute 34.64% of the total population of the sub city.

### Study population and inclusion criteria

All pregnant women with hyperemesis gravidarum, and pregnant women with the same gestational age but without hyperemesis gravidarum that fulfilled the inclusion criteria from the source population during the study period were involved. The inclusion criteria for the study group were hyperemesis gravidarum women with vomiting of three episodes per day without any obvious cause except for pregnancy, weight loss of 3 kg or 5% and the presence of at least one positive Ketonuria, age of 18 to 45 years, and gestation between five and 16 weeks. The controls were matched by maternal age, gestational age, parity and women without history of HG who volunteered to participate in the study. Pregnant women were not considered for the study if they had received antibiotics and women who have had other causes of vomiting such as hyperthyroidism, multiple gestation and gestational trophoblastic disease.

### Sample size and sampling technique

A total of 150 pregnant women, 50 cases with hyperemesis gravidarum and 100 controls without hyperemesis gravidarum with a 1:2 case to control ratio were studied. Convenient sampling technique was employed consecutively to include study participants who met the inclusion criteria. Stool, urine and blood sample collection was done until we achieved the expected sample size in the antenatal care department in each the study sites.

### Sample collection, processing and laboratory analysis

Socio-demographic data such as age, marital status, education level, occupation, and relevant clinical data such as parity, gravidity, gestational period, history of hyperemesis gravidum, history of gastrointestinal illness, water used for drinking, habits of hand washing before meals and after toilet use, habits of smoking, alcohol drinking, and Khat chewing were obtained using a predesigned questionnaire through interview by data collectors. Stool, urine and blood specimens were collected following standard procedures. Stool samples were used for parasite detection using direct smear microscopy and Formol-Ether stool sedimentation concentration technique. Stool samples were also used for *H. pylori* detection using HpSA test kit (CTK Biotech HpSA kit, San Diego, CA 92121 Inc., USA). Urine specimens were used for ketone body determination using strip tests and blood samples were used to determine complete blood count and hemoglobin concentration using automated Humacount Analyzer.

### Data management and quality assurance

Just before starting the actual research work, adequate training was given to data collectors and supervisors. All data collectors were adequately informed to check the completeness of each data before submission. Most importantly, data collection tools, laboratory SOPs and laboratory protocols were followed strictly and maintained throughout all procedures and were supervised and by principal investigator.

### Data analysis and interpretation

Data were entered using Microsoft Excel and analyzed with SPSS version 20, SAS version 9.4 and results were expressed using frequency and percentages. Chi square was done to identify factors associated with *H. pylori* infections followed by multi-variant analysis. Association between the prevalence of risk factors and *H. pylori* infections was assessed by $\chi^2$ tests. Quantitative data were expressed as mean ± standard deviation and range, using Student "t" test. Anemia was defined according to the WHO definition as a hemoglobin concentration of < 12 g/dL for adult women. Logistic regression was used to determine the effect of independent variables on the prevalence of *H. pylori* infections. In all cases, a 95% confidence interval was used and P-values less than 0.05 were considered as statistically significant.

## Results

### Sociodemographic characteristics of study subjects

A total of 150 adult women, 50 (33.3%) pregnant women with hyperemesis gravidarum and 100 (66.7%) pregnant women without hyperemesis gravidarum had participated in the study. The age of the study participants range from 18 - 40 years, with a mean (± SD) age of 28.0 (± 4.5) years for HG cases and 18 - 38 years, with a mean (± SD) age of 27.0 (± 4.4) for controls. In this study, there was no statistically significant difference between cases and controls in sociodemographic characteristics which includes marital status, education level, occupational status and number of siblings in the house (Table 1). There was no statistically significant difference between cases and controls with gestational age. However, there was statistically significant difference among groups in gravidity (Table 2).

| Characteristics Variables | Cases (n = 50) | Control (n = 100) | T | P value |
|---|---|---|---|---|
| **Age (in Years)** | | | | |
| Min. - Max. | 18-40 | 18-38 | | |
| Mean ± SD | 28.0 ± 4.5 | 27.0 ± 4.4 | | |
| Median | 28 | 27 | 1.438 | 0.153 |
| **Marital Status** | N (%) | N (%) | $X^2$ | |
| Married | 47 (33.6) | 93 (66.4) | | |
| Single | 3 (30) | 7 (70) | 0.054 | 0.559 |
| **Education Level** | | | | |
| Illiterate | 4 (30.8) | 9 (69.2) | | |
| Primary school | 11 (31.4) | 24 (68.6) | | |
| Secondary school | 20 (30.8) | 45 (69.2) | 1.153 | 0.768 |
| Higher education | 15 (40.5) | 22 (59.5) | | |
| **Occupational Status** | | | | |
| Government | 9 (31) | 20 (69) | | |
| NGO | 4 (50) | 4 (50) | | |
| Private | 19 (30.2) | 44 (69.8) | 2.446 | 0.650 |
| House wife | 18 (37.5) | 30 (62.5) | | |
| House maid | 0 (0) | 2 (100) | | |
| **Number of Siblings** | | | | |
| Two | 16 (30.8) | 36 (69.2) | | |
| Three | 7 (24.1) | 22 (75.9) | | |
| Four | 26 (41.3) | 37 (58.7) | 3.484 | 0.329 |
| Greater than four | 1 (16.7) | 5 (83.3) | | |

***Table 1:*** *Sociodemographic characteristics of cases and controls in selected healthcare facilities in Addis Ababa, Ethiopia; from July to October, 2016.*

*T: Student t-test, Fisher's exact test used for cells less than 5, NGO: Nongovernmental organization.*

| Characteristics | Cases (n = 50) | Control (n = 100) | $X^2$ | P value |
|---|---|---|---|---|
| **Gravidity** | **N (%)** | **N (%)** | | |
| First pregnancy | 20 (28.2) | 51 (71.8) | | |
| Second pregnancy | 24 (48) | 26 (52) | 7.778 | 0.020* |
| Greater or equal to three | 6 (20.7) | 23 (79.3) | | |
| **Gestational Period** | | | | |
| 1 - 12 week | 24 (28.8) | 59 (71.1) | | |
| 13 - 24 week | 26 (38.8) | 41 (61.2) | 1.632 | 0.225 |

***Table 2:*** *Obstetric history of cases and controls in selected healthcare facilities in Addis Ababa, Ethiopia; from July to October, 2016.*

**: Statistically significant.*

## Prevalence of *H. pylori* infection among cases and controls

In this study, the overall prevalence of *H. pylori* infection in all study participants was 24.7% (37/150). The prevalence of *H. pylori* infection was higher in cases than controls, 56% (28/50) vs. 9% (9/100) ($X^2$ = 39.626, P = 000), respectively (Table 3).

| *H. pylori* Serostatus | HG Group | Control Group | Total | $X^2$; P Value | OR; 95%CI |
|---|---|---|---|---|---|
| Positive | 28 [56%] | 9 [9%] | 37 [24.7%] | | |
| Negative | 22 [44%] | 91 [91%] | 113 [75.3%] | 39.626 | 12.869 |
| Total | 50 [100%] | 100 [100%] | 150 [100%] | <0.001* | [5.318 - 31.318] |

***Table 3:*** *H. pylori* serostatus among cases and controls in selected healthcare facilities in Addis Ababa, Ethiopia; from July to October, 2016.

**: Statistically Significant.*

In this study, there was a statistically significant difference between HG cases and controls with behavioral characteristics and associated risk factors which includes smoking habit, Khat chewing habit, history of hyperemesis gravidarum, history of gastrointestinal illness and anemia status. However, the numbers of study participants that responded to have smoking and Khat chewing habit were very low (Table 4).

| Characteristics | Cases (n = 50) | Control (n = 100) | $X^2$ | P value |
|---|---|---|---|---|
| **Habit of alcohol use** | **N, (%)** | **N, (%)** | | |
| Yes | 4 (50) | 4 (50) | | |
| No | 46 (32.4) | 96 (67.6) | 1.056 | 0.442 |
| **Smoking habit** | | | | |
| Yes | 3 (100) | 0 (0) | | |
| No | 47 (32) | 100 (68) | 6.122 | 0.036* |
| **Khat chewing habit** | | | | |
| Yes | 4 (100) | 0 (0) | | |
| No | 46 (31.5) | 100 (68.5) | 8.219 | 0.011* |

| | | | | |
|---|---|---|---|---|
| **Intestinal parasite** | | | | |
| Positive | 4 (66.7) | 2 (33.3) | | |
| Negative | 46 (31.9) | 98 (68.1) | 3.125 | 0.175 |
| **Water for drinking purpose** | | | | |
| Tanker | 2 (100) | 0 (0) | | |
| Pipe water | 48 (32.4) | 100 (67.6) | 4.054 | 0.110 |
| **History of gastrointestinal illness** | | | | |
| Yes | 28 (45.9) | 33 (54.1) | | |
| No | 22 (24.7) | 67 (75.3) | 7.308 | 0.008* |
| **History of hyperemesis gravidarum** | | | | |
| Yes | 50 (96.2) | 2 (3.8) | | |
| No | 0 (0) | 98 (100) | 141.3 | 0.000* |
| **Anemia status** | | | | |
| Anemic | 23 (71.9) | 9 (28.1) | | |
| Non anemic | 27 (22.9) | 91 (77.1) | 27.191 | 0.000* |

***Table 4:*** *Analysis of behavioral risk factors among cases and in selected healthcare facilities in Addis Ababa, Ethiopia; from July to October, 2016.*

**: Statistically significant. Fisher's exact test used for cells less than 5.*

## Comorbidity of *H. pylori* infection and anaemia in cases and controls groups

From all study subjects, 21.3% (32/150) were anemic, of which 71.9% (23/32) of anemic study subjects were found in the cases group. The remaining anemic 28.1% (9/32) were found controls group. Importantly, 56% (28/50) of cases and 9% (9/100) of controls were infected with *H. pylori* ($X^2$ = 5.547, p value = 0.024 (Figure 1).

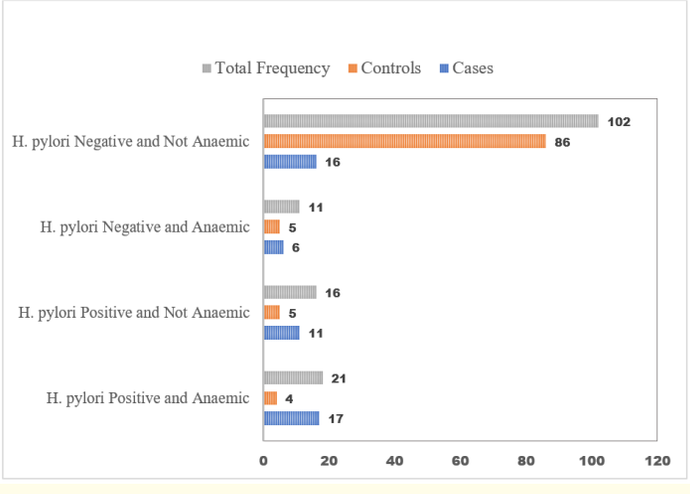


***Figure 1:*** *Showing comorbidity between H. pylori infection and anemia among cases and controls in selected healthcare facilities in Addis Ababa, Ethiopia; from July to October, 2016.*

## Discussion

It is estimated that *H. pylori* infection might be present in 50% of the global population. However, the pathogenic relationship between HG and *H. pylori* is not well established yet because most of those infected with *H. pylori* do not complain with symptoms. In other words, the presence of *H. pylori* can be asymptomatic. Furthermore, the problems in diagnosis of *H. pylori* infections are more complicated during pregnancy since HG could mask an active *H. pylori* infection or HG may be worsened by superimposed *H. pylori* infections [22]. However, data concerning the association of *H. pylori* infection and HG among pregnant women obtained through case control study particularly in Ethiopia was not available. In the current study, attempt was made to investigate the association, if any, between the severity of the disease and the presence of *H. pylori* using HpSA test.

In this study, the prevalence of *H. pylori* infection was higher in HG cases than in controls (which was 56% vs. 9% respectively and with a statistically significant level. Therefore, *H. pylori* infection has been found to be associated with HG women. A similar result were reported by Bezircioğlu İ., *et al*. in 2011 [23], Samy MD., *et al*. in 2016 [24], Elmahdy M., *et al*. in 2016 [25], Sandven., *et al*. in 2009 [26], Hatziveis K., *et al*. in 2007 [27], Nasr., *et al*. in 2012 [28], Kazerooni., *et al*. in 2002 [29], Guven., *et al*. in 2011 [30] and Hussein KS in 2020 [31]. However, Aytac., *et al*. in 2007 was reported a different result that described no association between *H. pylori* infection and HG and *H. pylori* could not be a risk factor for HG [32]. The most likely justification for the association of *H. pylori* infection and hyperemesis gravidum could be in early of pregnancy an increased accumulation of fluid and displacement of intracellular and extracellular volume could occur as a result of the increased steroid hormones, which in turn induces a change of pH and in the gastrointestinal tract this alteration of acidity could lead to the activation of a latent *H. pylori* infection [33,34]. This in turn could exacerbate mild to moderate dyspepsia commonly associated with nausea and vomiting symptoms that usually complicates most pregnancies [35,36].

On the other hand, the results of this study showed that there was no statistically significant difference between the HG group and the control group in terms of maternal age, marital status, educational level, occupational status, number of households. A similar finding was reported by Aytac., *et al*. in 2007 in Turkey [32] and Kazemzadeh M., *et al*. in 2014 [29]. However, Shirin H., *et al*. in 2004 found that women who had complaints of frequent vomiting in the first trimester and were positive for *H. pylori* IgG were significantly older than those who were negative for *H. pylori* IgG [37]. In addition, there was no statistically significant difference between patients and controls according to gestational age but there was significant difference between the two groups in gravidity. However, Elmhady M., *et al*. in 2016 and Samy MD., *et al*. in 2016 reported that there was no statistically significant difference in gravidity between cases and controls [24,25].

Regarding the behavioral characteristics and some expected associated risk factors like smoking habit, Khat chewing habit, history of hyperemesis gravidarum, history of gastrointestinal illness and anemia status showed statistically significant difference between the two groups. However, the numbers of study participants that respond having smoking and Khat chewing habit were very low. A recent study done by Hassan., *et al*. in 2015 in Kenya showed that Khat chewing was associated with *H. pylori* infection [38]. However, in our study the number of study subjects who responded habit of Khat chewing was very low in numbers. On a rather different finding, Vikanes., *et al*. in 2010 was reported that women who smoked daily or occasionally had lower risk of hyperemesis than nonsmokers [39].

In this study we observed a statistically significant difference between *H. pylori* infection and anemia; and *H. pylori* infection was higher in cases than controls. Thirty two of our study participants, (21.3%) were anemic and of these participants, 71.9% (23/32) of anemic pregnant women were from HG cases. In this study, *H. pylori* infection was associated with anemia (OR = 4.121, 95% CI = 1.233 - 13.771). Our findings agreed with other studies done by Bezircioğlu İ., *et al*. in 2011 [23]. Some possible mechanisms by which *H. pylori* affects iron metabolism include decreased absorption resulting from chronic gastritis, decreased gastric juice ascorbic acid concentration which is known to facilitate iron absorption [40], increased hepcidin production associated with *H. pylori* gastritis [33], uptake of iron by *H. pylori*

for growth [34], and decreased availability of iron by sequestration of iron into lactoferrin in the gastric mucosa [41]. Similar possible explanations in different studies have been hypothesized in *H. pylori* infection, and some of which are decreased as mucosal iron absorption capacity due to low gastric pH, reduction of stomach vitamin C levels, bacterium and host competition for dietary iron supply, lactoferrin mediated iron sequestration by gastric *H. pylori*, increased hepatocytes hepcidin release in response to Interlukin-6 production associated with *H. pylori* gastritis [3,30,42].

In general, our study suggested that there is a strong association between *H. pylori* infection and HG women. *H. pylori* infection was associated with a low hemoglobin value and higher rate of anemia in *H. pylori* infected HG pregnant women than pregnant women without HG. The result from this study could be used as a baseline to further investigate the role of *H. pylori* infection in the occurrence of anemia and HG in pregnant women and to take clinical measures to treat affected pregnant women.

## Conclusion and Recommendation

This study suggested that there was an association between *H. pylori* infection and pregnant women with hyperemesis gravidarum. Therefore, *H. pylori* could be considered as one of the risk factors for hyperemesis gravidarum in women during pregnancy. In addition, *H. pylori* infection was associated with low hemoglobin value and *H. pylori* infected hyperemesis gravidarum pregnant women showed higher rates of anemia than pregnant women without Hyperemesis gravidarum. Further primary care level studies recommended to further explore whether screening and eradication treatment of *H. pylori* infection could benefit the mother and the fetus during the course of pregnancy.

## Limitations of the Study

The results of this study need to be interpreted with considerations of certain limitations, as the determination of *H. pylori* infection was done only by one diagnostic method.

## Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Addis Ababa University, College of Health Sciences, School of Medical Laboratory Sciences. Permission letter was also obtained from each study facilities. In addition, all women who provided written and attended their antenatal care visit in the participating healthcare facility in Addis Ababa were included in this study. Moreover, all subject identifiers were delinked from the source file and anonymity of the study participants was ensured throughout data analysis.

## Data Availability

All data used in supporting the findings of this study could not be shared in publicly available repository platforms as there is no system to do so in Ethiopia. However, data could be accessed from authors upon written request.

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## Consent for Publication

All authors consent for publication.

## Conflict of Interest

The authors declare they do not have competing of interest.

## Authors Contributions

YA, GT and KD were involved from conception of idea, designing study protocol, data collection, data analysis and generating findings of the study. Drafting the manuscript and critically appraising in to the final manuscript write up for scientific content. All authors have read, edited and approved the manuscript.

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