



# Prevalence of *Helicobacter pylori* Infection among Anemic School-Age Children in Egypt: A Cross-Sectional Population-Based Study

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## Abstract

Anemia and *Helicobacter pylori* infection in school-age children are important public health problems. The association between *H. pylori* infection and the development of anemia, especially iron deficiency anemia, has been previously studied and until now it is still a matter of argument. This study aimed to determine the prevalence of anemia and *H. pylori* infection among school-age children and to find the association between *H. pylori* infection and anemia in school-age children. We conducted this population-based cross-sectional study in six Egyptian primary schools over a 12-month-period, including 1,200 students from all grades who fulfilled the inclusion criteria. The study participants were subjected to the following: medical history, clinical examination, and laboratory investigations included complete blood count and *H. pylori* antigen in stool, and according to the level of hemoglobin (Hb), we divided the students into two groups; the anemic group with Hb level <11.5 g/dL and nonanemic group with Hb level ≥11.5 g/dL, and the serum ferritin levels were measured only for the anemic group as the best indicator for iron status. The overall prevalence of *H. pylori* infection was 25%. The overall prevalence of anemia was 13.25%, of which hypochromic microcytic anemia represented 87.4% of the anemic group, and the mean ferritin level in the anemic group was 18.56 ± 9.96 ng/mL. The prevalence of anemia among *H. pylori*-infected patients (62.3%) was significantly ( $p < 0.001$ ) higher than in noninfected children (37.7%). In the anemic group, the mean ferritin level in *H. pylori*-infected children was significantly lower than the mean level in the noninfected children ( $p < 0.001$ ). Furthermore, the anemic group had a significantly higher incidence of *H. pylori* infection and a lower age ( $p < 0.001$ ) in comparison with the nonanemic group. The dominant type of anemia in *H. pylori*-infected children was the microcytic hypochromic anemia, with a significantly higher incidence in comparison to other types of anemia ( $p < 0.001$ ). The findings of this study demonstrate a significant association between *H. pylori* infection and anemia in school-aged children, especially iron deficiency anemia, as the incidence of *H. pylori* infection was greater in anemic children than in non-anemic children.

## Keywords

- ▶ anemia
- ▶ iron deficiency anemia
- ▶ *Helicobacter pylori* infection
- ▶ school-age children
- ▶ ferritin level

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## Introduction

Anemia is a global public health problem that corresponds to 24.8% of the population in both developing and developed countries and is assumed that 50% of the cases of anemia are due to iron deficiency (ID) but the proportion may vary among population groups and in different areas according to the local conditions.<sup>1</sup> The main risk factors for iron deficiency anemia (IDA) include a low intake of iron, poor absorption of iron, and gastrointestinal (GI) bleeding due to different causes like celiac disease, parasitic infestations, peptic ulcer, and *Helicobacter pylori* infection.<sup>2–4</sup>

Most *H. pylori* infections are usually without clinical manifestation, particularly in poor communities. However, signs and symptoms associated with the disease are primarily due to gastric or duodenal inflammation. *H. pylori* infection developed during early childhood has been reported to have extradigestive consequences including the retardation of growth rate, the development of ID, or both.<sup>5</sup>

The relationship between *H. pylori* infection and development of ID or IDA has been largely studied and until now it is still a matter of argument despite many studies and meta-analysis that concluded a solid relationship is not only between infection, either symptomatic or not, and development of IDA but also between the eradication of infection and improvement of iron status in the subjects. On the other hand, some studies denied a relationship between infection with *H. pylori* and IDA.<sup>6</sup>

Meta-analyses of population studies suggest the contribution of ID to anemia could be smaller than the World Health Organization (WHO) estimate: 25% in children and 37% in women and because of the paucity of population studies measuring iron biomarkers (beyond hemoglobin [Hb]) and complexities in their interpretation during inflammation, prevalence estimates of ID in low-income countries are uncertain.<sup>7</sup>

In Egypt, there is no reliable evidence or national registry about the prevalence of *H. pylori* infection or anemia in school children and, apart from individualized efforts, there are no national records about the scope of these two problems. Although there has been much research on low Hb concentrations and anemia worldwide, most of this has focused on children aged <5 years (0–59 months) and pregnant women; data for school-age children are sparse. This study aimed to detect the prevalence of anemia including IDA and *H. pylori* infection in school-age children in Sharqia governorate in Egypt and the relationship between these two problems because it is essential to uncover the hidden causes of anemia to effectively control anemia in this country.

## Subjects and Methods

### Study Design, Population, and Sampling Techniques

We conducted this cross-sectional population-based study during the academic year 2017 to 2018 in primary schools in Sharqia governorate, Egypt. Sharqia governorate is the third most populous of the governorates of Egypt located in the

northern part of the country. Its capital is the city of Zagazig. We listed all educational administrative departments at the Sharqia governorate. From the total educational administrative departments of Sharqia governorate, Zagazig educational administrative department was selected randomly by a lottery method then all primary schools located in Zagazig educational administrative department, including urban and rural areas, are listed from A to Z (from the first to the last one) and a random selection of 6 primary schools using a lottery method. All children from all grades in the six selected primary schools aged from 6 to 12 years were eligible for this study. According to local authority guidelines, regular yearly stool analysis for every student in primary school is done to detect parasitic infestations and regular deworming of school-age children in its control strategy. Regular deworming treatment reduces the intensity of infection and gives protection to those already infected.<sup>8</sup>

### Inclusion and Exclusion Criteria

Following an initial screening, children with a history of *H. pylori* eradication or antacid use, ongoing iron therapy, liver disease or diabetes, with malformations or serious chronic diseases, inflammatory bowel disease or previous GI surgery, and ongoing parasitic infestations were excluded from the study. This study included a total of 1,200 students from all grades in the six selected primary schools, based on sample size calculation with Power Analysis and Sample Size Software.

### Data Collection

All students that fulfilled the inclusion criteria were subjected to the following: medical history, clinical examination with special emphasis on manifestations of anemia (pallor, fatigue, irritability, palpitation, shortness of breath, pica, tachypnea, tachycardia, and koilonychia), and *H. pylori* infection (nausea, vomiting, loss of appetite, and chronic abdominal pain that was defined by the American Academy of Pediatrics' 2005 clinical report as long-lasting intermittent or constant abdominal pain that is functional or organic with a minimum duration of 3 months),<sup>9</sup> and laboratory investigations included complete blood count (CBC) and *H. pylori* antigen in stool. According to the level of Hb, we divided the students into two groups: Anemic group with Hb level <11.5 g/dL and non-anemic group with Hb level ≥11.5 g/dL based on the WHO definition of anemia published in 2011,<sup>10</sup> and the serum ferritin level was done only for the anemic group as the best indicator for iron status.<sup>11,12</sup>

*H. pylori* antigen in stool is a noninvasive method with good sensitivity and specificity, 94% and 97% respectively in the global meta-analysis, in the diagnosis of *H. pylori* infection.<sup>13</sup>

### Specimen Collection and Processing

Peripheral blood samples were collected and divided into two tubes: 1 mL on ethylenediamine tetraacetic acid tube for CBC and 1 mL on a heparinized tube; centrifuged plasma was separated and preserved at  $-20^{\circ}\text{C}$  until the time of assay. Stool samples were preserved at  $-20^{\circ}\text{C}$  until the time of

the assay. The blood and stool samples collection staff included clinical nurses and laboratory technologists, under the supervision of general practitioners. CBC was performed by Sysmex cell counter kx-21 made in Japan. Serum ferritin was measured by using enzyme immunoassay for qualitative determination of ferritin in human plasma/serum (catalogue No.pt-ferr 96 manufactured by Pishtaz Teb Diagnostic—European authorized representative ID consulting services Ltd. Korbach, Germany). *H. pylori* antigen was performed by enzyme-linked immunosorbent assay for quantitative assay of *H. pylori* Ag in human stool specimen using the kit manufactured by Immunospec Corporation (Canoga, California, United States) (reference catalogue No. E32–320 referred by European Authorized Representative: CE partner4U, the Netherlands).

### Ethical Consideration

To start this study, written consent was obtained from the child's parents and the nature, and the aim of our study was explained to them. The study was approved by the ethical consideration committee in Institutional Review Board after taking the permission of local authorities.

### Statistical Analysis

Data were collected and analyzed by SPSS version 20.0. Quantitative data were expressed as mean  $\pm$  standard deviation. Qualitative data were expressed as frequency and percentage. Independent-samples *t*-test of significance was used when comparing two means. Chi-squared ( $X^2$ ) test of significance was used to compare proportions between two qualitative parameters. *p*-Value  $\leq 0.05$  was considered significant while *p*-value  $\leq 0.001$  was considered highly significant.

### Results

A total of 1,200 students (620 boys and 580 girls) from six primary schools were enrolled in the study. The mean age of the children was  $8.62 \pm 1.69$  years. *H. pylori* infection prevalence was 25% (300/1200). The mean Hb level was  $12.79 \pm 1.15$  g/dL and the overall prevalence of anemia was 13.25%. The microcytic hypochromic anemia accounted for 87.4% of the anemic group, and the mean ferritin level in the anemic group was  $18.56 \pm 9.96$  ng/mL. The clinical manifestations related to anemia or *H. pylori* infection were also shown in ►Table 1.

In comparison with the nonanemic group, the anemic group had a significantly higher incidence of *H. pylori* infection diagnosed by stool antigen test, chronic abdominal pain, pallor, and a lower age ( $p < 0.001$ ). However, regarding sex, no significant difference between anemic and nonanemic groups was observed. The prevalence of anemia among *H. pylori*-infected was 0.33, and the prevalence of anemia among noninfected was 0.066, so the prevalence ratio is 4.95. Based on this ratio, the proportion of children with anemia is 4.95-fold greater if the child is infected with *H. pylori* (►Table 2).

The infected children showed a significantly higher incidence of pallor ( $p < 0.001$ ) and recurrent abdominal pain

**Table 1** Demographic and laboratory characteristics of all students enrolled in the study

Variable	Frequency	Percent
Age (N = 1200)		
<9 y	608	50.7
$\geq 9$ y	592	49.3
Range	6–11.5	
Mean $\pm$ SD	$8.62 \pm 1.69$	
Sex (N = 1200)		
Males	620	51.7
Females	580	48.3
<i>H. pylori</i> antigen in stool (N = 1200)		
Infected children	300	25
Noninfected children	900	75
Anemia (N = 1200)		
Anemic group	159	13.25
Nonanemic group	1041	86.75
Types of anemia (N = 159)		
Microcytic hypochromic	139	87.4
Normocytic normochromic	3	1.9
Macrocytic	17	10.7
Clinical manifestations (N = 1200)		
Pallor	292	24.33
Chronic abdominal pain	680	56.7
No manifestations	228	19.03
Hb g/dL (N = 1200)		
Mean $\pm$ SD	$12.79 \pm 1.15$	
Ferritin level in the anemic group (ng/mL)		
(n = 159)	4 - 33	
Range	$18.56 \pm 9.96$	
Mean $\pm$ SD		

Abbreviation: SD, standard deviation.

( $p < 0.05$ ) and lower levels of Hb, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and hematocrit (HCT) in comparison with the non-infected children ( $p < 0.001$ ) (►Table 3).

In the anemic group, the mean ferritin level in *H. pylori*-infected children was  $15.33 \pm 8.80$  ng/mL and the mean level in the noninfected children was  $20.51 \pm 10.15$  ng/mL, with a significant difference between *H. pylori*-infected and noninfected children ( $p < 0.001$ ) (►Table 4).

In the infected children, the dominant type of anemia was microcytic hypochromic anemia, with a significantly higher incidence in comparison to other types of anemia ( $p < 0.001$ ) (►Table 5).

### Discussion

Various epidemiological studies conducted all over the world have shown an association between *H. pylori* infection and IDA. The association between *H. pylori* infection and the development of anemia, especially IDA, has been previously

**Table 2** Comparison between the two groups according to *Helicobacter pylori* infection and clinical characteristics of all students enrolled in the study ( $n = 1,200$ )

		Groups		Total	Test	p-Value
		Nonanemic group ( $n = 1,041$ )	Anemic group ( $n = 159$ )			
Age (y)	< 9 y	481 (46.2%)	127 (79.9%)	608 (50.7%)	$\chi^2 = 62.5$	<0.001 <sup>a</sup>
	≥ 9 y	560 (53.8%)	32 (20.1%)	592 (49.3%)		
	Mean ± SD	8.78 ± 1.66	7.35 ± 1.33	8.62 ± 1.69	$t = -10.3$	<0.001 <sup>a</sup>
Sex	Male	549 (52.7%)	77 (48.4%)	626 (52.2%)	$\chi^2 = 1.02$	NS
	Female	492 (47.3%)	82 (51.6%)	574 (47.8%)		
<i>H. pylori</i> antigen in stool	Noninfected children	840 (80.6%)	60 (37.7%)	900 (75%)	$\chi^2 = 137.8$	<0.001 <sup>a</sup>
	Infected children	201 (19.4%)	99 (62.3%)	300 (25%)		
Chronic abdominal pain	No	477 (45.8%)	43 (27.0%)	520 (43.3%)	$\chi^2 = 19.8$	<0.001 <sup>a</sup>
	Yes	564 (54.2%)	116 (73.0%)	680 (56.7%)		
Pallor	No	868 (83.4%)	40 (25.2%)	908 (75.7%)	$\chi^2 = 253.9$	< 0.001 <sup>a</sup>
	Yes	173 (16.6%)	119 (74.8%)	292 (24.3%)		

Abbreviation: SD, standard deviation.

<sup>a</sup>Statistically highly significant difference ( $p \leq 0.001$ ), NS; not significant.Note:  $\chi^2$ , Chi-squared test;  $t$ , Student's  $t$ -test.**Table 3** Comparison between *Helicobacter pylori*-infected and noninfected children regarding laboratory and clinical parameters ( $n = 1,200$ )

CBC and clinical parameters		<i>H. pylori</i> infection		Test	p-Value
		Infected ( $n = 300$ )	Noninfected ( $n = 900$ )		
Hb	Mean ± SD	12.24 ± 1.11	12.66 ± 0.59	$t = -8.4$	< 0.001 <sup>b</sup>
MCH	Mean ± SD	24.25 ± 3.22	25.51 ± 2.21	$t = -7.4$	< 0.001 <sup>b</sup>
MCV	Mean ± SD	77.39 ± 9.10	78.99 ± 5.79	$t = -3.5$	< 0.001 <sup>b</sup>
HCT	Mean ± SD	33.9 ± 1.52	39.2 ± 2.12	$t = 30.14$	<0.001 <sup>b</sup>
Pallor	No	180 (60%)	724 (80.5%)	$\chi^2 = 47.8$	<0.001 <sup>b</sup>
	Yes	120 (40%)	176 (19.5%)		
Chronic abdominal pain	No	110 (36.6%)	409 (45.4%)	$\chi^2 = 7.3$	<0.05 <sup>a</sup>
	Yes	190 (63.4%)	491 (54.6%)		

Abbreviations: CBC, complete blood count; Hb, hemoglobin; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; SD, standard deviation.

<sup>a</sup>Statistically significant difference ( $p \leq 0.05$ ).<sup>b</sup>Statistically highly significant difference ( $p \leq 0.001$ ).Note:  $\chi^2$ , Chi-squared test;  $t$ , Student's  $t$ -test.**Table 4** Comparison between *Helicobacter pylori*-infected and noninfected children regarding the ferritin level in the anemic group ( $n = 159$ )

	<i>H. pylori</i> infection		$t$	p-Value
	Infected ( $n = 99$ )	Noninfected ( $n = 60$ )		
Ferritin level in the anemic group (ng/mL) ( $n = 159$ )				
Mean ± SD	15.33 ± 8.800	20.51 ± 10.15	3.2	<0.001 <sup>a</sup>

<sup>a</sup>Statistically highly significant difference ( $p \leq 0.001$ ).Note:  $t$  refers to Student's  $t$ -test.

**Table 5** Types of anemia in *Helicobacter pylori*-infected children ( $n = 99$ )

Types of anemia in <i>H. pylori</i> -infected children ( $n = 99$ )	$n$	%	$X^2$	$p$ -Value
Microcytic hypochromic	87	87.9	133.4	<0.001 <sup>a</sup>
Normocytic normochromic	3	3		
Macrocytic	9	9.1		

<sup>a</sup>Statistically highly significant difference ( $p \leq 0.001$ ).

Note:  $X^2$  refers to Chi-squared test.

studied and until now it is still a matter of argument. Consequently, new programs designed to decrease the prevalence of ID and IDA in high-risk groups may necessitate eradicating *H. pylori* infection.<sup>14</sup>

*H. pylori* colonization of the stomach persists in some individuals for a long time and is closely related to gastritis, duodenal ulcers, and extra-GI disorders, including IDA, in childhood.<sup>15</sup> ID is common in all populations, but particularly devastating for pregnant women, young children, and those with the greatest requirements. ID is associated with increased vulnerability to infections and permanent cognitive impairment, particularly among school-age children. IDA negatively affects cognitive functions and psychomotor development.<sup>16</sup>

The prevalence of anemia and *H. pylori* infection is unequally distributed among different populations; so, in this study, we aimed to evaluate the prevalence of *H. pylori* infection and anemia among school children and to evaluate the association between *H. pylori* infection and anemia. The results of this study revealed that the overall prevalence of *H. pylori* infection was 25%. This finding was consistent with the findings of Zamani et al<sup>17</sup> who found a prevalence of *H. pylori* infection in 26% of Iranian primary school children and Naous et al<sup>18</sup> who found a prevalence of *H. pylori* infection of 21% in asymptomatic Lebanese pediatric patients. Furthermore, in a study conducted in Turkey between 2013 and 2014 with 2 to 18-year-old children, the *H. pylori* infection prevalence rate was 30.7%.<sup>19</sup> This was consistent with the epidemiological studies in Poland, which evaluated *H. pylori* seroprevalence and reported that 32.0% of children below 18 years of age were infected.<sup>20</sup>

In contrast to findings of this study, a higher prevalence of *H. pylori* infection among Egyptian children was reported in studies conducted by Galal et al, Deeb et al, Abdulkawi et al, and Mohammad et al (64.6, 44, 68, and 72.4%, respectively).<sup>21–24</sup>

Our finding in terms of the prevalence of *H. pylori* infection was not consistent with a study conducted by Hasosah et al<sup>25</sup> who reported that the prevalence of *H. pylori* infection among symptomatic children in Saudi Arabia was 49.8%. According to Iwańczak et al,<sup>26</sup> there was a higher prevalence of *H. pylori* infection in Ethiopian children (48%), Nigeria (82%), Mexico (43%), and Bulgaria (61.7%).

On the other hand, many studies reported a lower prevalence of *H. pylori* infection in sub-Saharan Africa (14.2%), Iran

(13.1%), the United States (7.5%), Italy (8.7%), Japan (1.8%), Australia (15.5%), Canada (7.1%), the Netherlands (1.2%), and Sweden (3–13.6%).<sup>22,26–28</sup>

This variability in *H. pylori* infection rates between different studies is due to differences in the study design, geographic areas, target population, population inclusion, exclusion criteria, sample size, and *H. pylori* detection methods.<sup>13</sup>

The relatively low prevalence of *H. pylori* infection in this study could be due to *H. pylori* detection methods, as antibody testing procedures for *H. pylori* detection are used in some studies that lead to false high results and do not differentiate between past or active infection. Our study employed an *H. pylori* stool antigen testing method because of its noninvasive nature and effectiveness especially in children. Spontaneous *H. pylori* infection clearance has been observed due to exposure to antibiotics to treat other infections in childhood, the period during which antibiotics are widely used, and spontaneous eradication has been associated with several variables and has been reported to be higher in children receiving iron supplements for ID.<sup>13,28–30</sup>

The relatively low prevalence of *H. pylori* infection in this study could be also due to the autocurability and the reinfection phenomena, as Zhou et al<sup>28</sup> have documented that the annual autocurability rate was 2.9% among the pediatric population.

With regard to Hb level in this study, we did not anticipate these results, including the mean Hb level ( $12.79 \pm 1.15$  gm/dL) and the prevalence of anemia (13.25%), and the microcytic anemia accounted for 87.4% of the anemic group. The prevalence of anemia among school children in this study was comparable with the results of other similar studies among school children in Indonesia (13%),<sup>31</sup> Addis Ababa (the capital city of Ethiopia) (15.5%),<sup>32</sup> and Turkey (15.7%).<sup>33</sup> In China, a significant decrease in the prevalence of anemia was observed from 12.6% in 2002 to 6.6% in 2010 to 2012.<sup>34</sup>

In contrast to our study results, higher trends have been described in population-based studies among young children in Egypt that reported a higher prevalence of anemia like Mansour et al<sup>35</sup> who stated that 53.1% of the school children were anemic and a survey conducted by Salama and Labib, earlier in three Egyptian governorates (Fayoum, Beni Suef, and Minia), reported that the prevalence of anemia was 59.3%.<sup>36</sup> Also, other studies conducted among Egyptian school children reported that the prevalence of anemia was 38.7 and 39.9%.<sup>1,37</sup> The global anemia prevalence was 47.4% in preschool-age children and ~25% of school-age children as reported by Gonete et al (25.5%),<sup>38</sup> Ngui et al (26.2%),<sup>39</sup> and Oliveira et al (21.6%).<sup>40</sup>

Based on the WHO report, anemia affects 45.7 to 49.1% of school-age children in the world, and the prevalence of anemia among school-age children in Africa ranged from 64.3 to 71%.<sup>41</sup>

Contrary to expectations, our findings indicated lower anemia prevalence in school-age children, and this can be explained in many ways, including the exclusion criteria of



our study: any child with a history of liver disease or diabetes, with malformations or serious chronic diseases, inflammatory bowel disease or previous GI surgery, and parasitic infestations. The Hb concentration cutoff for anemia definition in this study was relatively high (11.5 g/dL) in comparison to other studies that reported Hb concentration cutoff was 10 to 11.5 g/dL.

Another reason for a relatively low anemia prevalence in school-age children in this study is the national program of iron supplementation in our country that was implemented before the study and the mass media for increasing knowledge about the danger of anemia and lastly, the efforts done by the ministry of health in Egypt for early detection of anemia in early life as all infants are examined for Hb level at the age of 1 year during the routine scheduled examination and vaccination program. The American Academy of Pediatrics suggests a routine screening for IDA for all children at the age of 12 months by using Hb concentration.<sup>42</sup>

In 2008, the Egyptian government began implementation of a 5-year national program to fortify the wheat flour used in baking subsidized baladi bread with iron and folic acid.<sup>43</sup> The WHO author panel reported that 7.1 mg/day of ferrous sulfate fortification of flour is moderately effective, whereas 11 mg/day is highly effective. The Egyptian program corresponds to this highly effective category, and it is predicted by the panel that a highly effective program might reduce ID prevalence in at-risk populations to levels seen in industrialized countries. Many campaigns have used iron supplements, especially in schools, to combat ID and malnutrition.<sup>44</sup>

The mean ferritin level in this study in the anemic group was  $18.56 \pm 9.96$  ng/mL. Furthermore, less than 15  $\mu$ g/L ferritin is specific for ID, whereas less than 30  $\mu$ g/L ferritin is highly suggestive (lower ferritin thresholds for ID diagnosis in children: <10–12 ng/mL) but when inflammation exists, the WHO defines ID at a ferritin level less than 30  $\mu$ g/L in children under 5 years and less than 70  $\mu$ g/L in older children. The WHO estimates that 50% of anemic cases worldwide are due to ID.<sup>45</sup>

There was no significant difference between anemic and nonanemic groups regarding sex in this study with no plausible explanation and this came in agreement with other studies that have shown no significant difference in the mean Hb concentration between boys and girls.<sup>46–49</sup> However, other studies have shown that the mean Hb concentration is generally higher in boys than girls.<sup>50,51</sup>

Microcytic hypochromic anemia accounted for 87.4% of the anemic group in this study. Similarly, Maiti et al<sup>52</sup> stated that microcytic hypochromic anemia was the most prevalent (71.3%) morphologic type of anemia in children, and other studies reveal incidence varying between 45 and 70%.<sup>53,54</sup>

Our studied groups followed the normal distribution curve regarding the age and there is a marked significant difference between anemic and nonanemic children regarding the age with 79.9% of anemic children who were below 9 years old; so the prevalence of anemia is much higher in the first three grades in primary school children and this may be explained by feeding habits of Egyptian families that contain more cereals and fewer iron supplementations affecting

more the lower ages, who did not follow the correct feeding programs after school entrance.

In the anemic group, this study revealed that the mean ferritin level in *H. pylori*-infected children was significantly lower than the mean level in the noninfected children. Furthermore, the anemic group had a significantly higher incidence of *H. pylori* infection in comparison with the nonanemic group, so there was an association between infection with *H. pylori* and not only the development of anemia but also iron status in the body.

These study findings, in terms of the significance of association between *H. pylori* infection and anemia in school-age children, were consistent with a study conducted by Mourad-Baars et al<sup>55</sup> who reported a significant association between *H. pylori* and IDA in children, and the treatment of *H. pylori* infection showed an increase in Hb level in 65% children without iron supplementation. So, *H. pylori* eradication therapy combined with iron administration showed an increase in Hb level in 75% children that is more effective than iron administration alone for the treatment of IDA.

Similarly, Hassan et al<sup>56</sup> revealed that there was a significant increase in the number of positive samples for *H. pylori* antigen in stool among anemic versus nonanemic controls and a significant association between children with IDA and positive *H. pylori* infection in school-age children. Baggett et al<sup>57</sup> suggested that infection with *H. pylori* may contribute to ID and IDA among children in countries where these conditions are highly prevalent.

A recent systematic review reported that, in observational studies, compared with uninfected persons, *H. pylori*-infected individuals are at greater risk for ID and IDA, and clinical trials have shown that combined treatment of *H. pylori* eradication and iron supplementation results in a larger serum ferritin increase than iron supplementation alone.<sup>58</sup>

In contrast to this study's results, Zahmatkeshan et al<sup>59</sup> and Sarker et al<sup>60</sup> reported no correlation between IDA and *H. pylori* infection in school-age children in Iran and Bangladesh, respectively. In addition, a few studies reported no significant association between serum ferritin level or IDA and antibody titer against *H. pylori* bacteria in school-age children.<sup>17,61,62</sup>

In this study, there was a statistically highly significant difference between anemic and nonanemic groups with regard to chronic abdominal pain and pallor. At the same time, there was a statistically highly significant difference between *H. pylori*-infected and noninfected groups with regard to pallor and a statistically significant difference regarding chronic abdominal pain. Consequently, a coincidence of pallor as a manifestation of anemia with recurrent abdominal pain as a manifestation of *H. pylori* infection may highlight the need for studying the relationship between anemia and *H. pylori* infection as causation not only an association.

Hassan et al<sup>56</sup> found an association between *H. pylori* infection and GI disorders such as recurrent abdominal pain. In our study results, dyspepsia, chronic gastritis, and peptic ulcers were associated with *H. pylori* infection and suggested that *H. pylori* infection is more frequently associated with gastritis than with peptic ulcer disease in children. *H. pylori*

gastritis is a cause of recurrent abdominal pain syndrome in children.

Concerning CBC parameters (Hb, MCV, MCH, HCT), there was a statistically highly significant difference between *H. pylori*-infected and noninfected groups and there was a statistically highly significant difference between types of anemia. Microcytic hypochromic anemia is the most common type (87.9%) in *H. pylori*-infected group in this study. This was consistent with El-Kady et al<sup>63</sup> who reported that *H. pylori* infection significantly affected the Hb level, MCV, MCH, and red blood cells distribution width in studied cases. Meanwhile, *H. pylori* infection significantly affected the serum iron, serum ferritin, and total iron-binding capacity (TIBC) in studied cases of IDA.

Similarly, several studies highlighted that after confirmation of eradication of *H. pylori*, the mean values of Hb and iron indices including ferritin have improved significantly without the use of iron supplementation that indicates improved absorption of dietary iron with subsequent improvement in IDA.<sup>64,65</sup>

Many studies showed a significant reduction was observed in the levels of serum Hb, iron, and ferritin among infected children with *H. pylori* compared with noninfected ones as this study proved.<sup>66–69</sup>

In contrast to these study results, Soyulu and Ozturk<sup>70</sup> conducted a study in Imam Reza Hospital of Mashad on 184 patients. No significant difference was detected between the average serum ferritin level of the *H. pylori* infected group and control group. Also, Sh and Al-Ani<sup>71</sup> stated that there was no significance between *H. pylori* infection and age, weight, height, platelets, red blood cells, Hb, MCV, MCH, ferritin, and iron. Haghi-Ashtiani et al<sup>72</sup> found no relationship between *H. pylori* infection and IDA. However, Hoseinzadeh et al<sup>73</sup> found a significant negative correlation of *H. pylori* antibody level with serum iron and ferritin and its positive correlation with TIBC levels.

The causes of ID and/or low iron absorption during *H. pylori* infection have been attributed to several mechanisms, such as microbleeding and/or iron uptake affection, which may deplete iron stores in patients even without ulcer disease. Also, *H. pylori* requires iron for its growth; it expresses proteins associated with iron metabolism and decrease in mucosal iron absorption capacity due to reduced gastric acid output, competition of the bacterium with the host for the dietary iron supply, reduction in the gastric juice vitamin C content in infected subjects, increased hepcidin production from hepatocytes in response to IL-6 production associated with *H. pylori* gastritis, or sequestration of iron in lactoferrin in the gastric mucosa. Consequently, *H. pylori*-positive subjects before treatment had a smaller increase in serum iron compared with *H. pylori*-negative subjects, and after *H. pylori* eradication in the *H. pylori*-positive subjects, their serum iron increase was similar to those of noninfected subjects, suggesting that *H. pylori* infection impairs oral iron uptake as in Hassan et al<sup>56</sup> and Chiu et al<sup>74</sup> studies.

Regarding the presence of macrocytic anemia in *H. pylori*-infected children, Gravina et al<sup>75</sup> stated that

decreased absorption of vitamin B12 in the case of *H. pylori* infection might be due to intrinsic factor deficiency, which is damaged in the case of *H. pylori*-related corpus-predominant gastritis and several meta-analyses clearly showed a strong association between *H. pylori* infection and IDA. According to tertiary referral hospital laboratory results, the vitamin B12 levels in patients with macrocytic anemia in our study were low that necessitate treatment with vitamin B12 and treatment of associated *H. pylori* infections. In addition, a correlation between *H. pylori* infection and low serum levels of vitamin B12, which increased after *H. pylori* eradication, may be another reason for anemia caused by *H. pylori*.<sup>76</sup>

The study had strength points including that such information about anemia and *H. pylori* infection is of greatest importance to public health authorities before any action regarding these problems can be undertaken. Based on the prevalence of *H. pylori* infection and anemia, it is recommended that screening and treatment programs for *H. pylori* among anemic children in socially deprived areas be considered as a way forward in tackling these problems.

Due to methodological issues, our study has limitations that we measured serum ferritin level in the anemic children only and did not investigate for subclinical inflammation or infection that leads to elevation of serum ferritin levels, exclusion criteria of the study, and this may lead to underestimation of the proportion of anemic children with ID. The cross-sectional design of this study limits inference about the causal relationship between *H. pylori* infection and anemia. Furthermore, the association between anemia and *H. pylori* infection raises concerns about confounding by unmeasured exposures. Additionally, the *H. pylori* stool antigen could not be compared with a gold standard test to diagnose *H. pylori* infection. Finally, our study was conducted in a single city, which may limit the generalizability of our findings.

Considering the results of this study, it is recommended to prioritize the development of diagnostic methods and treatments for *H. pylori* in Egypt. We should carefully consider appropriate interventions to eradicate *H. pylori*, to improve anemia status. In children with unexplained IDA, *H. pylori* testing and treatment may be clinically indicated and a combination of *H. pylori* eradication therapy and iron therapy may increase ferritin and Hb levels. We should screen high-risk children with pallor and abdominal pain using *H. pylori* stool antigen, CBC, and ferritin to identify those children for which treatment of *H. pylori* and IDA would lead to reduce the prevalence and associated short- and long-term consequences.

## Conclusion

According to this study, *H. pylori* infection was found in 25% of school-age children, and anemia was reported in 13.25% of them, with microcytic hypochromic anemia being the most common type. The results of this study demonstrate also a significant association between *H. pylori* infection and anemia including IDA in school-age children as the prevalence of

*H. pylori* infection was higher among anemic children when compared with nonanemic.

#### Authors' Contributions

M.A., T.A.A., and E.G.B. designed the study, collected, and interpreted data, and wrote the manuscript. M.A., T.A.A., E.G.B., and D.H. collected, evaluated the patient's interpreted data, and wrote the manuscript. All the authors evaluated the patient's interpreted data and wrote the manuscript. All the authors critically contributed to the discussion and data interpretation, reviewed, and approved the final manuscript.

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#### Conflict of Interest

None declared.

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