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Editorial

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This is the fifth issue this year that is rich with papers from the region of interest to primary care physicians. Tawfig, et al., did a cross-sectional survey on 128 mothers who came for children's vaccination at primary health care centers using a structured questionnaire in form of dichotomous, multiple choice, and open and scaling questions. The aim to analyze mothers' breastfeeding knowledge, attitudes, and practices, as well as factors that impact EBF at 6 months. Of all mothers, 80.5% previously received information about breastfeeding. Of them, 38 (29.7%) initiated breastfeeding within 1 h of delivery. The authors concluded that EBF for up to 6 months was not recommended despite the high percentage of mothers who initiated breastfeeding right after birth or within a few hours. Sustained health and community-based nutritional education are recommended for pregnant and lactating mothers to promote optimal breastfeeding for the initiation and continuation of breastfeeding practices. More counseling and support are needed for working mother

Chaudry & Almarsomi, reviewed the role of glucagon-like peptide-1 analogues in weight management. They stressed that obesity is a growing concern in all parts of the world. It carries major health concerns which are in turn translated to financial costs. Alongside patient education and guidance, both surgical and pharmacological methods are being employed to control weight. A major breakthrough in this regard has been introduction of glucagon-like peptide-1 analogues (GLP-1), which have now been approved for use in weight management.

Jawa et al., looked at the prevalence of colonic diverticulosis among adult patients with obesity and metabolic syndrome conditions. 342 patients diagnosed with diverticulosis and confirmed by colonoscopy and CT scan were included with age above 18 years old receiving a health examination, measurement of percentage of body fat, blood test and colonoscopy. Women with body mass index (BMI \geq 30) had a greater risk developing diverticulosis (PR, 1.58; 95% CI, 1.05–2.06) when compared to women with

normal BMI. by gender, in patients less than fifty-one, occurrence of colonic diverticulosis was less in female patients compared to male ones (29% vs 45%, $P=.06$). The authors concluded that the risk of colonic diverticulosis has an obvious correlation to obesity specially in women whose BMI \geq 30. When comparing by age, colonic diverticulosis was less predominant in premenopausal-age women compared with similar-age men. These findings may be due to female sex hormones that enhance diverticulosis development.

Ali et al., followed a multi-center retrospective descriptive electronic record-based study for all subjects with a valid ultrasound of the ovaries done in PHCC health centers from 1 January 2021 to 31 December 2021. The aim of this study is to estimate the prevalence and ultrasound features of PCOS among young females. The current study showed prevalence of PCO among young female with age ranging from 15 to 35 years to be 6.85% with majority of cases being bilateral. While unilateral cases were more at right ovary. The authors concluded that Ultrasound plays a major role in PCO diagnosis. The assessment of the ovaries has been greatly improved by sonographic diagnostic criteria of PCO. In addition to demonstration of ovarian size, ultrasonography can evaluate the characteristic patterns of follicles distribution and ovarian stromal changes.

Hakami, et al., reviewed Venous Thromboembolism Awareness Among Saudis Risk Group at Primary Health Care Centers in Riyadh. VTE is an outcome from an inequity of hemostasis and thrombosis. It is important to note that VTE is a disease of complex nature that occurs within families. Genetic as well as acquired risk factors play an important role in its occurrence. VTE risk assessment and prophylaxis constitute part of the preventive tools that can be utilized at health care providers level. Therefore, reviewing whether VTE risk status has been established and administering approved VTE prophylaxis are accepted to be the central healthcare provider role. Healthcare practitioners ought to identify patients at risk

of developing VTE and select the appropriate therapy, thus reducing its incidence. In addition, to the PE's risk of death, DVT frequently results in a post-thrombotic syndrome that lowers quality of life. Therefore, VTE prevention is an area that could be targeted to promote health and safety not only in healthcare settings, but also community.

Dr. Islam., reviewed the challenging task of improving eradication rates of *Helicobacter pylori* in light of rising antibiotic resistance. *Helicobacter pylori* (*H. pylori*) infection continues to be a major public health issue worldwide. A global systematic review shows that in 2015, approximately 4.4 billion individuals worldwide were estimated to be positive for *H. pylori*. Factors such as density of housing, overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher acquisition rate of *H. pylori* infection. The problem of recurrence of *H. pylori* infection after successful treatment also appears closely associated with socioeconomic and sanitary conditions.

Farooq, et al., conducted a cross-sectional analytical study for a duration of 9 months in Lahore, Pakistan. Study included 150 fertile and 150 infertile females aged 18-45. The aim is to evaluate the Doppler indices of uterine and ovarian arteries in fertile and infertile women and help clinicians develop more effective diagnostic and treatment strategies for infertility. Age of participants range between 19 to 43 years. Independent sample test showed statistical significance between RI and PI of right ovarian artery of both groups ($P < 0.05$). However, in left ovarian artery the values of PI in both groups showed a significance ($P < 0.05$) were as values RI are found to be insignificant ($P > 0.05$). Independent sample test showed statistical significance between RI and PI of right and left uterine artery of both groups ($P < 0.05$). The mean + SD endometrial thickness in fertile group was 11.0 + 2.6 mm it was 9 + 1.6 mm in infertile group (Table 3). Indicating a significant difference between the two groups ($P < 0.05$). The authors concluded that Uterine

and Ovarian artery hemodynamics plays an important role in fertility. Findings from this study revealed that a high RI and PI and thin endometrium significantly affects fertility.

Khattak et al., looked at the Effect of COVID-19 lock down on development of infants and toddlers. The COVID-19 lockdowns played a major role in restricting growth of disease(1) and that saved many lives.(2) However, COVID-19 lockdowns had some major drawbacks too. There was a significant impact on economy (2) and it undoubtedly affected the development of infants and toddlers in multiple ways. This paper looks at impact of COVID-19 lockdown on infants and toddlers.

Helvaci et al looked at the proportion that acute painful crises may be causes of sudden deaths in sickle cell diseases.

They concluded that the hardened RBCs-induced capillary endothelial damage, inflammation, edema, and fibrosis are initiated at birth, and terminate with disseminated tissue hypoxia and multiorgan failures even at childhood in the SCDs. Although RBCs supports and corticosteroids in acute phase and aspirin plus hydroxyurea both in acute and chronic phases decrease severity of the diseases, survivals are still shortened in both genders, dramatically. Infections, medical or surgical emergencies, or emotional stresses-induced increased basal metabolic rate aggravates the sickling and capillary endothelial edema, and may terminate with acute painful crises, multiorgan failures, and sudden deaths.

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Exclusive breastfeeding for the first six months after birth: A cross-sectional study in health care centers in Khartoum, Sudan

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Walid Tawfig, Lateefa Othman Aldakhil. Exclusive breastfeeding for the first six months after birth: A cross-sectional study in health care centers in Khartoum, Sudan. World Family Medicine. June 2023; 21(5): 6-12

DOI: 10.5742/MEWFM.2023.95256105

Abstract

Background: Encouraging exclusive breastfeeding (EBF) practices for the first 6 months of life is the most effective intervention for lowering childhood morbidity and death. However, compliance with breastfeeding recommendations is lacking in many developing countries. Thus, this study aimed to analyze mothers' breastfeeding knowledge, attitudes, and practices, as well as factors that impact EBF at 6 months.

Methods: This cross-sectional survey was conducted on 128 mothers who came for children's vaccination at primary health care centers using a structured questionnaire in form of dichotomous, multiple choice, and open and scaling questions.

Results: Of all mothers, 80.5% previously received information about breastfeeding. Of them, 38 (29.7%) initiated breastfeeding within 1 hour of delivery. Of the participants, <50% knew (46.1% and 44.5%, respectively) about breastfeeding, and 92.2% of mothers (118) had a negative view of EBF. The length of EBF for 1–2 months, 3–4 months, and 5–6 months were 3.9%, 82.8%, and 13.3%, respectively. Other foods are introduced before 6 months of age because of insufficient breast milk (15.6%) and the mother has work (11.7%).

Conclusion: EBF for up to 6 months was not recommended despite the high percentage of mothers who initiated breastfeeding right after birth or within a few hours. Sustained health and community-based nutritional education are recommended for pregnant and lactating mothers to promote optimal breastfeeding for the initiation and continuation of breastfeeding practices. More counseling and support are needed for working mothers.

Key words: exclusive breastfeeding, first six months, Khartoum, Sudan

Introduction

Breastfeeding is the most cost-effective method of infant feeding as it provides the infants with the required nutrition in the safest way. Breast feeding has been shown to decrease the risk of sudden infant death syndrome, childhood cancer, bronchial asthma, infectious diseases (otitis media, pneumonia, gastroenteritis), obesity, and diabetes(1-6). It is estimated that optimal breastfeeding practices prevent 13% of deaths among under-fives. Mothers who breast feed are at lower risk of breast cancer, anemia, and osteoporosis(6).

The World Health Organization (WHO) and almost all other international health bodies have recommended exclusive breastfeeding (EBF) for the first 6 months after birth. Based on the WHO guidelines, breastfeeding is classified into three categories: exclusive breastfeeding, predominant breastfeeding, and partial breastfeeding(8,9). EBF is when the infant had received only breast milk from the mother, a wet nurse, or expressed breast milk and no other liquids or solids except for drops of syrup consisting of vitamins, mineral supplements, or medicines. Predominant breastfeeding is when the infant's predominant source of nourishment had been breast milk. However, the infant may receive water and water-based drinks, such as tea and local herbal drops. Partial breastfeeding is when the infant's feeding could include non-breast milk foods, such as animal or powdered condensed milk and/or solid or semisolid food (i.e., cereals, vegetables, fruits, lentils, or meat) (10,11).

WHO growth standard recognizes the importance of EBF for healthy growth and development of children(12). Foods, other than breast milk, should not be introduced before the age of 6 months because they may be harmful. Malnutrition and stunting of growth affect more than half of children under 5 years of age in underdeveloped nations, and it typically begins in infancy, probably caused by inappropriate breastfeeding and mixed feeding patterns(13,14).

The prevalence of EBF for the first 6 months of life is extremely low despite strong evidence to support it, and the prevalence varies from country to country and society to society, depending on cultural and religious beliefs, but it is generally low worldwide. Between 2007 and 2014, only 36% of infants were exclusively breastfed between the ages of 0 and 6 months (15,16). Delayed breastfeeding initiation, colostrum deprivation, supplementary feeding of breast milk substitutes, early introduction of complementary feeding, and incorrect weaning from breast milk are commonly found practices in communities worldwide(17–19).

Global Breastfeeding Collective of United Nations International Children's Emergency Fund (UNICEF)/WHO aims to increase the percentage of exclusively breastfed babies under 6 months old from 44% to 70% by 2030. The initiation and continuation of EBF will be achieved when a mother is physically and psychologically prepared and supported and informed about the benefits of breastfeeding practices(7,10).

Breastfeeding cessation before 6 months is caused by different factors, including the return to work, low socioeconomic status, low educational level, inconvenience or fatigue associated with breastfeeding, and insufficient milk supply(20-23). Awareness has played a role in compliance with the initiation and continuation of EBF. Findings from smaller studies indicate that breastfeeding intent is associated with a positive breastfeeding attitude(24-26).

The duration of breastfeeding in urban affluent mothers is shorter compared to others, thereby demonstrating its presence as a matter of public health importance(23). This study examined the factors affecting EBF in the first 6 months of life in Khartoum where exclusive breast feeding is the most cost-effective way of infant feeding(7).

Materials and Methods

Study setting

This cross-sectional qualitative study conducted from December 2021 to January 2022 included mothers who visited the vaccination clinics at two primary health centers near Khartoum City. Sampling was done on mother/child pairs using the Cochran formula. The minimum number of participants required for inclusion in the sample group was calculated as 196 based on a 95% confidence interval of $(x + 0.05)$.

Inclusion criteria were mothers with a child from 6 months through to 5 years old and living in the study areas. Exclusion criteria were conditions where breastfeeding is contraindicated, such as galactosemia and mothers suffering from cancer, active tuberculosis, and psychosis. Questions were written and administered in Arabic and translated into English for analysis. Two experts in the research methodology field reviewed the survey and provided their feedback. Pilot testing of the questionnaire was conducted on 15 participants to ensure good reliability and validity of the instruments. The survey was revised according to all inputs. The questionnaire included mother and child characteristics (socio-demographic status and birth-related events), the practice of breastfeeding, and knowledge and attitude toward EBF.

We adhered to the WHO recommendations to define the nursing pattern(27). We focused on the first 6 months after delivery(28). EBF is when babies only received milk from their mother or a wet nurse without other food except for syrup medication. A baby that is exclusively breastfed is solely given breast milk for sustenance, and no water and water-based beverages, such as tea or regional herbal drops, are given. The newborn also consuming non-human milk feeds, such as animal milk, formula milk, vegetable soup, lentils, or other solid or semisolid foods, was referred to as partial breastfeeding. Full (exclusive or predominant) and partial breastfeeding were the two categories of the primary outcome variable, which measured breastfeeding patterns.

Age, education, and employment of the mother; socioeconomic standing; religion; caste stratification; family structure; birth order; gender; birth weight; gestational age; delivery method; and site of delivery of the child were among the demographic factors included as predictors. The timing of breastfeeding initiation, colostrum feeding, pre-lacteal feeding, self-reported breastfeeding issues, and knowledge of the suggested time frame for EBF were all factors connected to breastfeeding practices.

Results

A total of 737 children attended the two medical care centers where this study was conducted, with their mothers during the study period for different consultations or vaccines. This study included 128 infants with their mothers who met the study inclusion criteria and who agreed to participate in the study. Of the infants, 66 were males while 62 were females. Additionally, 37 (28.9%) were >24 months old and 91 (71.1%) were <24 months old. The majority of children (90%) were >2.5 kg at birth. Of the mothers, 86 (70%) have a high education level; 60 (47%) are workers, 20 (1%) are students, and 48 (37%) are housewives; 84 (66%) had a middle- or high-income level according to their perception. All but 1 of the 128 mothers reported having visited the antenatal clinics during the last pregnancy. However, only 25 (19.5%) mothers mentioned not getting information about the importance of breastfeeding during their antenatal visit or before/after this study anywhere.

The majority (126 [98%]) of mothers initiated breastfeeding within the first 24 hours of delivery, and 111 (87%) exclusively breastfed their babies at 2 months which decreased to 106 (82.8%) at 4 months. However, only 17 (13.3%) exclusively breastfed at 6 months.

Table 1 demonstrates the distribution of certain characteristics of the mother in the form of EBF practice. Data revealed that mothers with college-level and higher education exclusively breastfed their babies to a greater extent than those who were educated to middle school. Housewives were more likely to breastfeed their babies at 4–6 months compared to working mothers. A similar significant finding was observed among families with lower income and women who received antenatal education.

Regarding the workplace environment, 25.0% (32) of the mothers were provided a private place to express breastmilk while 32.0% (41) had none.

Table 2 demonstrates the rate of EBF among different infant factors, with only the mode of delivery as the significant factor. Table 3 shows the multivariate analysis of the maternal/fetal factors which influence EBF for 1–2, 3–4, and 5–6 months. Significant factors in predicting EBF at 4 and 6 months were high educational levels, unemployed mothers (housewives), low income, and mothers who received antenatal education.

Other foods were introduced within the 6 months after delivery in the majority of respondents mainly because of perceptions related to breast milk sufficiency in 65% of mothers (lack of breastmilk, excessive crying, and not gaining enough weight), approximately 30% of mothers provided no reasons, followed by 11.7% of mothers who resumed work. The majority of participants are knowledgeable about the benefit of breastfeeding, and 93% of mothers knew that breast milk is the ideal food for babies, especially in the first 6 months. Further, 82% of mothers perceived that breast milk is more easily digested than formula and 85.2% reported that breast milk contains all the essential nutrients for a newborn child.

Only 33% have a positive attitude toward breastfeeding, and the majority agree that formula feeding is a better choice if the mother intends to resume work and women should not breastfeed in public places.

Table 1: Mother characteristics concerning EBF at 1, 3, and 6 months

Mother Characteristics						
<i>Independent variables related to the mother</i>	<i>0-1</i>	<i>Exclusive breastfeeding</i>			<i>Total</i>	<i>P-value</i>
		<i>2 months</i>	<i>4 months</i>	<i>6 months</i>		
Educational Level						
<i>No Education (% of total)</i>	<i>0</i>	<i>0</i>	<i>2(1.6%)</i>	<i>2 (1.6%)</i>	<i>4</i>	<i>0.019*</i>
<i>Low Education (% of total)</i>	<i>5(4%)</i>	<i>2(1.6)</i>	<i>19(14.8%)</i>	<i>4 (3%)</i>	<i>30</i>	
<i>High Education (% of total)</i>	<i>12(9.4)</i>	<i>3(2.3%)</i>	<i>68 (53%)</i>	<i>11 (8.6)</i>	<i>94</i>	
Work Status						
<i>Housewife (% of total)</i>	<i>0</i>	<i>3(2.3%)</i>	<i>35(27.3%)</i>	<i>10 (7.8%)</i>	<i>48</i>	<i>0.013*</i>
<i>Student (% of total)</i>	<i>6</i>	<i>2(1.6%)</i>	<i>10 (7.9)</i>	<i>2 (1.6%)</i>	<i>20</i>	
<i>Employee (% of total)</i>	<i>11</i>	<i>0</i>	<i>44(34.4%)</i>	<i>5 (4%)</i>	<i>60</i>	
Household Income as Perceived by Participants						
<i>Low (% of total)</i>	<i>7(5.5)</i>	<i>5(4%)</i>	<i>20 (16%)</i>	<i>12 (9.4)</i>	<i>44</i>	<i>0.042*</i>
<i>Medium–High (% of total)</i>	<i>10 (7.9)</i>	<i>0</i>	<i>69 (54%)</i>	<i>5 (3.9%)</i>	<i>84</i>	
Antenatal Education for EBF						
<i>Yes (% of total)</i>	<i>8(6.3%)</i>	<i>3(2.3%)</i>	<i>81 (69.5%)</i>	<i>11 (8.6%)</i>	<i>103</i>	<i>0.021*</i>
<i>No (% of total)</i>	<i>9(7%)</i>	<i>2 (1.6%)</i>	<i>8 (6.3%)</i>	<i>6 (4.7%)</i>	<i>25</i>	

Table 2: Baby characteristics concerning EBF at 1, 3 and 6 months

Baby Characteristics						
<i>Independent variables related to the baby</i>	<i>0-1</i>	<i>Exclusive breastfeeding for:</i>			<i>Total</i>	<i>P-value</i>
		<i>1–2</i>	<i>3–4</i>	<i>5–6</i>		
		<i>months</i>	<i>months</i>	<i>months</i>		
Type of Delivery						
<i>Normal Vaginal (% of total)</i>	<i>10(8%)</i>	<i>3(2.3%)</i>	<i>79(62%)</i>	<i>10 (7.8%)</i>	<i>102</i>	<i>0.063</i>
<i>Caesarian (% of total)</i>	<i>7(5.5%)</i>	<i>2 (1.6%)</i>	<i>10 (8%)</i>	<i>7 (5.5%)</i>	<i>26</i>	
Birth of The Baby						
<i>≥2.5 kg (% of total)</i>	<i>13(10%)</i>	<i>5 (3.9%)</i>	<i>81 (63 %)</i>	<i>16 (12.5%)</i>	<i>115</i>	<i>0.872</i>
<i><2.5 kg (% of total)</i>	<i>4 (3%)</i>	<i>0</i>	<i>8(6%)</i>	<i>1</i>	<i>13</i>	
Gender of The Baby						
<i>Boy (% of total)</i>	<i>9(7%)</i>	<i>3(2%)</i>	<i>48 (37.5%)</i>	<i>6 (4.7%)</i>	<i>66</i>	<i>0.221</i>
<i>Girl (% of total)</i>	<i>8(6%)</i>	<i>2 (1.5%)</i>	<i>41 (32%)</i>	<i>11 (8.5%)</i>	<i>62</i>	
Initiation of Breastfeeding						
<i><1 hour (% of total)</i>	<i>5(3.9%)</i>	<i>0</i>	<i>33 (25.8)</i>	<i>12 (9.3)</i>	<i>50</i>	<i>0.093</i>
<i>Within 24 Hours (% of total)</i>	<i>12(9.3)</i>	<i>3(2%)</i>	<i>56 (43.8)</i>	<i>5(%)</i>	<i>77</i>	
<i>More than 24 hours (% of total)</i>	<i>0</i>	<i>2(1.5%)</i>	<i>0</i>	<i>0</i>	<i>2</i>	

Table 3: Factors associated with exclusive breastfeeding at 1, 3, and 6 months in multivariate analysis

Independent variables related to the mother and infant	Exclusive breastfeeding for:				ARR	95% CI interval	P-Value
	1-2 months	3-4 months	5-6 months	Total			
EDUCATIONAL LEVEL							
No Education (% of total)	1	1	2	4	0.73	0.49-1.01	<0.001
Low education (% of total)	11	7	10	28	0.96	0.79-1.18	
High Education (High and above)	13	11	72	96	1.05	0.86-1.29	
WORK STATUS							
Housewife (% of total)	4	19	25	48	1.24	0.96-1.62	0.007
Student (% of total)	3	4	11	18	0.98	0.76-1.29	
Employee (% of total)	15	16	31	62	5.72	0.50-6.01	
HOUSEHOLD INCOME AS PERCEIVED BY PARTICIPANTS							
Low (% of total)	16	19	20	55	1.06	0.80-1.40	0.009
Medium-High (% of total)	19	20	34	73	0.99	0.58-1.71	
ANTENATAL EDUCATION FOR EBF							
Yes (% of total)	28	29	46	103	0.61	0.25-1.51	<0.001
No (% of total)	8	7	10	25	1.20	0.91-158	

ARR: adjusted odds ratio

Results

EBF through the first 6 months is the goal of The Global Breastfeeding Collective of UNICEF/WHO. Understanding the local practice, knowledge, and attitude is the first step in achieving such a goal. Many maternal and fetal factors could influence successful EBF continuation, and these factors may differ from one community to another. These factors could be related to education, socioeconomic status, and availability of support. Our data revealed that only 13.3% of the participants continue EBF through 6 months while the worldwide reported rate is <38% (29). Developed countries reported that a minority of infants are exclusively breastfed at 6 months (40% in the Netherlands; 13% in the USA) (30,31).

Of our 128 participants, 38 (29.7%) initiated breastfeeding within the first hour after birth, which was lower than a cross-sectional survey conducted in Ethiopia at 57.2%(10). The number increases to 126 (98%) mothers within the first 24 hours. The majority of mothers exclusively breastfed their babies at 4 months which decreased to only 13% at 6 months. The mother's perception of milk insufficiency is the major cause for introducing formula milk, followed by 30% without any reason for introducing other food before 6 months. This low rate of breastfeeding is one of the lowest rates in developing countries. The rate of EBF is 41% in North Africa, 44% in Asia, and 30% in Latin America. Despite

the recognizable economic benefits of breastfeeding, the breastfeeding practice, particularly EBF, is reported in only 25% of infants in Africa(31).

Our data revealed that the factors associated with the increased rate of breastfeeding continuation are high education level, unemployment, high socioeconomic status, and perinatal breastfeeding classes, similar to previous reports(32–34).

A meta-analysis of over 100 publications about breastfeeding initiation and continuation revealed only six significant factors, including maternal smoking, vaginal delivery, multiparity, dyad separation and connection, maternal education level, and breastfeeding education or support(35). Our study revealed a quite rare maternal smoking that is usually not declared, and the mode of delivery was not a significant factor for breastfeeding continuation although it was a significant factor in breastfeeding initiation. Breastfeeding initiation did not increase the possibility of EBF continuation by 6 months among our participants which was reported as a significant factor in other reports(36).

Mothers of poor socioeconomic status are less likely to practice EBF through 6 months of age which is a similar finding from other studies(37). Social determinants shape individual interaction and play a significant role in the well-being of the individual, family, and community (38). Cross-sectional data

from a study in Nigeria looked into inequality concerning EBF and estimated the proportion of linear population redistribution of EBF practices to eliminate the inequality (achieving zero inequality) and found that only 10.7% redistribution was needed to eliminate the inequality. Attendance of at least four antenatal clinic visits was the most significant contributor to the inequality in EBF practice(39). This study revealed that the majority of the mothers had good knowledge about breastfeeding but had a negative attitude toward it. Misconception, customs, and pseudo beliefs regarding breastfeeding practices remained prevalent in this community which needs to be addressed. Similarly, findings from smaller studies indicate that breastfeeding intent is associated with positive breastfeeding attitudes and having family, peer, and partner support, while others found prenatal factors, such as an increased number of prenatal visits and having a breastfeeding mother influence the decision to breastfeed(40).

It was found that mothers who attended breastfeeding classes were significantly more likely to practice EBF during the first six months of life, and most mothers introduced other foods before they reached the age of six months because they lacked knowledge or support. Previously published data (20) support the same finding of our study, which indicates no clear reason for discontinuing breastfeeding before 6 months, which is mainly related to a lack of motivation and support, wherein not many centers continue education and support as strong as in antenatal and early post-natal periods. Our data revealed that while most of the mothers had a good knowledge of breastfeeding, they had poor attitudes and wrong practices toward it.

Conclusion

Continued education and support for mothers and families will influence the EBF practice. This can be done via formal and informal education, as well as the availability of antenatal support after delivery, especially for the first year.

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Prevalence and ultrasound features of polycystic ovaries in young females examined by pelvic ultrasound in primary health care in Qatar. Electronic Medical record-based study

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Ali TF and Abougazia AS. Prevalence and ultrasound features of polycystic ovaries in young females examined by pelvic ultrasound in primary health care in Qatar. Electronic Medical record-based study.

Electronic Medical record-based study. World Family Medicine. June 2023; 21(5): 13-20

DOI: 10.5742/MEWFM.2023.95256106

Abstract

Background and study aim: PCOS is a common recognized, heterogeneous disorder affecting women throughout their lifetime and it shows an excess production of androgens hormone, ovulatory dysfunction and polycystic changes of the ovaries which can be seen by ultrasonography.

Ultrasound is the first imaging modality widely used in pelvic imaging. It is a non-invasive, rapid, painless, and safe imaging technique with no radiation.

The aim of this study is to estimate the prevalence and ultrasound features of PCOS among young females.

Patients and Methods: A Multi-center retrospective descriptive electronic record-based study for all subjects with a valid ultrasound of the ovaries done in PHCC health centers from 1 January 2021 to 31 December 2021.

The available pelvic ultrasound images were assessed for presence of PCOS sonographic criteria.

Prevalence of PCO was calculated. The sonographic features of PCO were described.

Results: The current study showed prevalence of PCO among young female with age ranging from 15 to 35 years, to be 6.85% with the majority of cases being bilateral. While unilateral cases were more in the right ovary.

Cases with PCO peripheral follicular arrangement were found to be the highest described sonographic finding in PCO cases.

Conclusion: Ultrasound plays a major role in PCO diagnosis. The assessment of the ovaries has been greatly improved by sonographic diagnostic criteria of PCO. In addition to demonstration of ovarian size, ultrasonography can evaluate the characteristic patterns of follicles distribution and ovarian stromal changes.

Key Words: Prevalence, PCO, US, Pelvis, Qatar.

Abbreviations:

PCO: polycystic ovaries.

PCOS: Polycystic ovarian syndrome

US: ultrasound

LH: luteinizing hormone

PHCC: primary health care corporation.

Background

Polycystic ovarian syndrome (PCOS) is a condition of ovarian dysfunction that was first described by Stein and Leventhal in 1935 when they described a group of women with amenorrhea, hirsutism, and enlarged ovaries with multiple cysts. Currently, PCOS is a common recognized, heterogeneous disorder affecting women throughout their lifetime and it shows an excess production of androgens hormone, ovulatory dysfunction and polycystic changes of the ovaries which can be seen in ultrasonography (1-10).

PCOS is now the most common reproductive endocrinal abnormality in women during their childbearing years and is considered as an endocrine disorder which can be attributed to a combined factor of genetic and environmental nature with many risk factors reported. On the top is obesity, sedentary lifestyle together with familial history (1-3, 10-17).

The European Society of Human Reproduction (in Rotterdam) and the American Society of Reproductive Medicine has proposed some criteria to establish the diagnosis of PCOS, that is in the presence of two of the following: Oligomenorrhea or amenorrhea, clinical features, or/and biochemical signs of hyperandrogenemia/hyperandrogenism, and sonographic findings of polycystic ovarian changes (2-4).

Transvaginal ultrasound (TVUS) is considered the gold standard in the diagnosis of PCOS. The sonographic features include increased number of follicles per ovary; the follicles are generally of similar size and their diameter ranges from 2-9 mm; follicles are peripherally distributed giving a "string of pearls" appearance; increased ovarian volume (>10mL) and echogenic dense central stroma (2,15).

Qatar is experiencing a fast development with mega projects that has led to a high influx of migrants and professionals from different countries resulting in a multi-ethnic young adult population with continuous and high demographic turnover (18). This would reflect substantially on the epidemiology and clinicopathologic characteristics of Qatar's prevalent diseases. To date, to the best of our knowledge there no similar study has been conducted to estimate the prevalence and ultrasound features of PCOS in Qatar.

Ultrasound is the first imaging modality widely used in pelvis imaging. It is a non-invasive, rapid, painless, and safe imaging technique with no radiation. The vision of PHCC is to be the leader in transforming the health and wellbeing of people's lives in Qatar. The corporation provides pelvic ultrasound services in most of its health centers and one of the important referral reasons of pelvic ultrasound is the evaluation of endocrine abnormalities, including polycystic ovaries.

Aim of the work:

The aim of this study was to estimate the prevalence and ultrasound features of PCOS among young females subjected to pelvis ultrasound in PHCC and to recognize the sonographic features of PCOS.

Patients and Methods

A multi-center retrospective descriptive electronic record-based study for all subjects with a valid ultrasound of the ovaries done in PHCC health centers from 1st January 2021 to 31st December 2021.

Study Population

- Inclusion criteria:

The inclusion criteria of the study was young females (15 to 35 years) who underwent a pelvis ultrasound scan in PHCC Radiology Departments for any reason. A valid pelvis ultrasound scan image should be available on the official PHCC electronic medical record system (RIS PACS system) during the study period from 1st January to 31st December 2021.

- Exclusion criteria:

The exclusion criteria was (as documented on CERNER) patients with non-available ovarian ultrasound images, history of surgery on the ovaries or any ovarian masses.

The available pelvis ultrasound images were assessed for presence of PCOS sonographic criteria.

A positive PCO case was considered in the presence of two of the following: Oligomenorrhea or amenorrhea, clinical features, or/and biochemical signs (hyperandrogenemia/hyperandrogenism) and sonographic findings of polycystic ovarian changes (2-4).

A random sample of 100 scans was evaluated by the two consultant radiologists participating in this study to determine the percentage agreement among them and document the validity of diagnosis reported.

The results of ultrasound images assessment by a study team member radiologist were recorded and compared immediately with the original radiologist report available. If the opinion of the reviewing radiologist agreed with that available in the attached report, then the data was verified and signed off. If there was a discrepancy between the two, then a third opinion was needed from the other research team member.

The one-year prevalence rate (per 100 persons) of positive PCOS was calculated:

Prevalence = $\left(\frac{\text{Count of subjects with a positive PCO}}{\text{Count all subjects evaluated with a valid ultrasound scan}} \right) \times 100$.

The data was delivered in an Excel sheet. Statistical analysis was computed using IBM SPSS version 23 computer software.

Results

The current study included 8,635 young females with age ranging from 15 to 35 years who were subjected to pelvis ultrasound in PHCC from 1st January to 31st December 2021. Polycystic ovaries were detected at ultrasound in 591 cases (6.85%), in 75.6% of cases they were bilateral while 24.4% were unilateral. Unilateral cases affected right ovary in 64.6% while left ovary was the only one involved in 35.4%.

Cases with PCO at right ovary showed ovarian volume of more than 10 cc in 79%, follicles number of more than 12 in 81%, dense stroma in 79.4% and peripheral follicular arrangement in 89.8%.

Cases with PCO at left ovary showed ovarian volume of more than 10 cc in 75.3%, follicles number of more than 12 in 83%, dense stroma in 76.7% and peripheral follicular arrangement in 88.6% (Table 1, Figures 1-4).

Table 1:

US Criteria	Right Ovary	Left Ovary
Volume >10 CC	79%,	75.3%
Follicles >12	81 %	83 %
Dense Stroma	79.4 %	76.7%
Peripheral follicular arrangement	89.8%	88.6%.

Figure 1 : Distribution of unilateral PCO (RO: right ovary, LO: left ovary)



Figure 2: Distribution of sonographic features of PCO in right ovary.

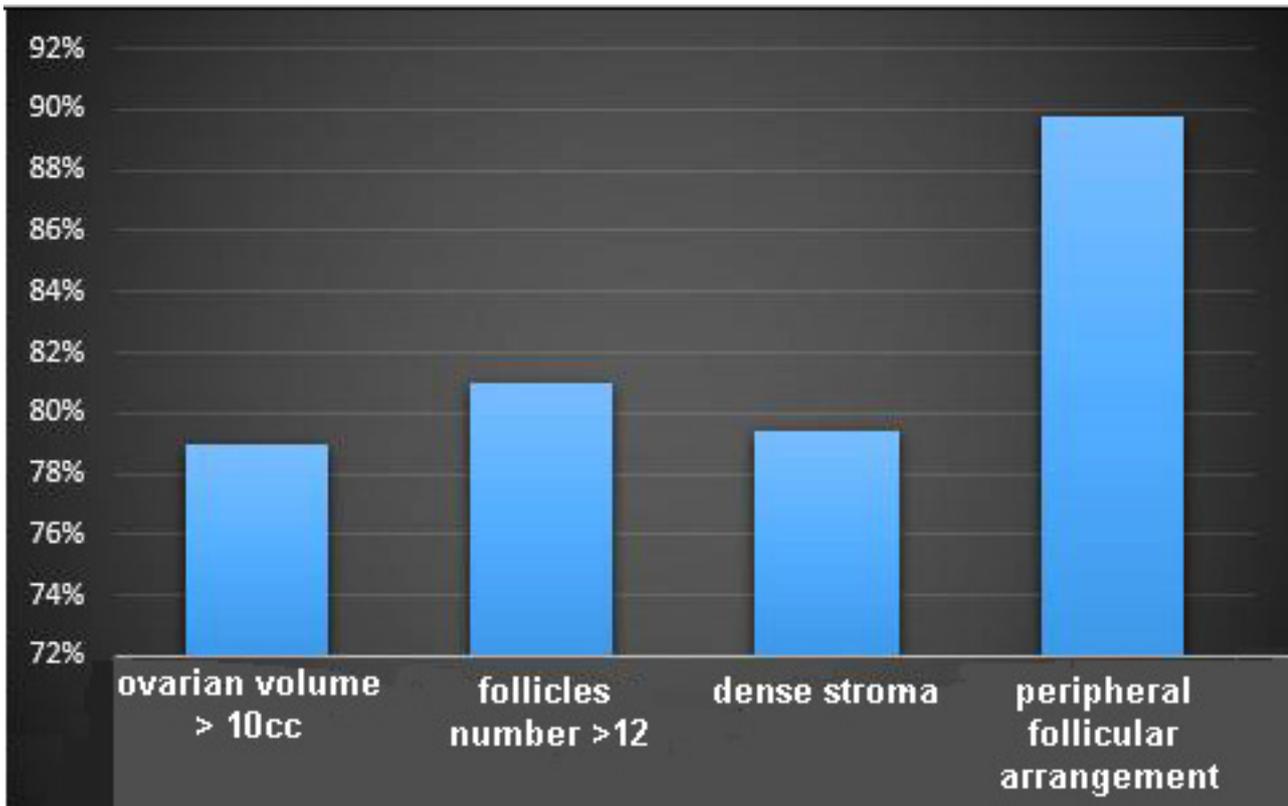


Figure 3: Distribution of sonographic features of PCO in left ovary.

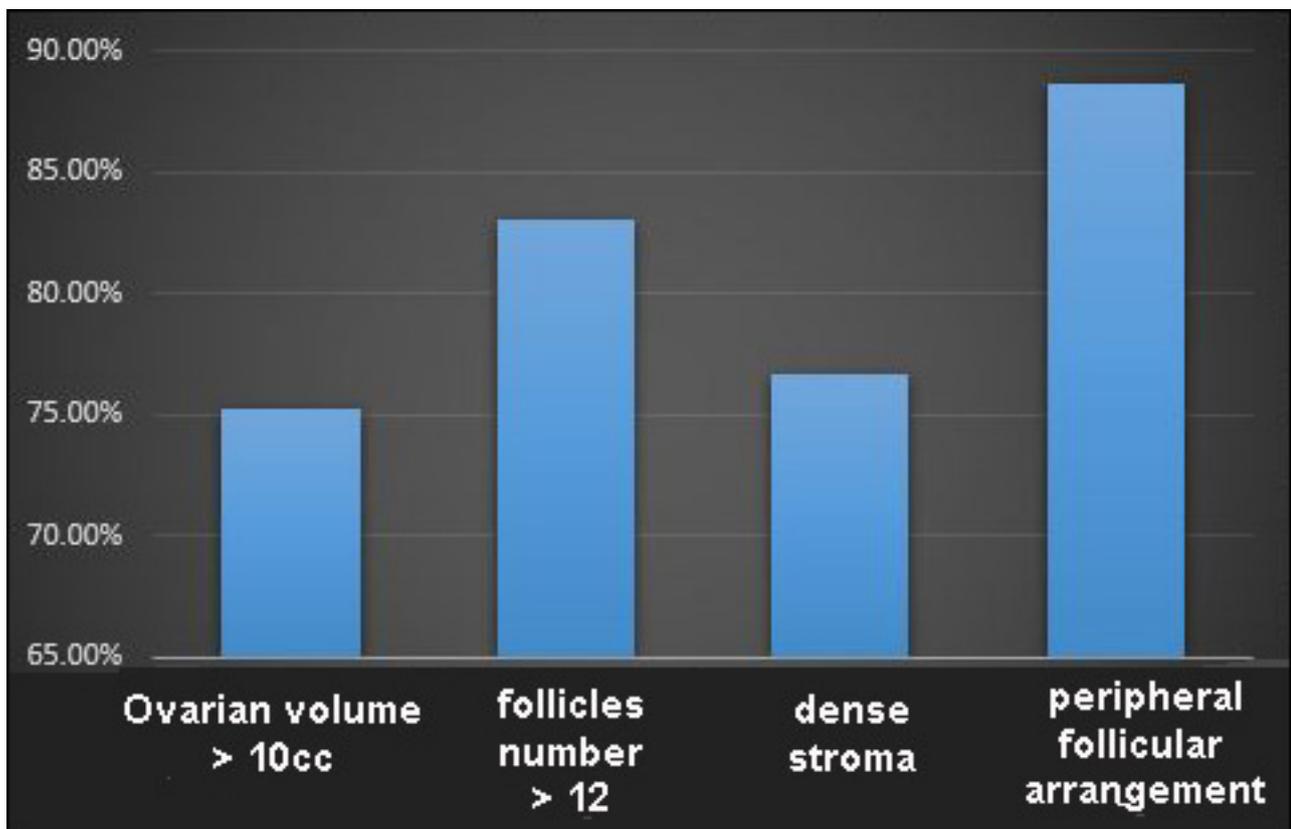
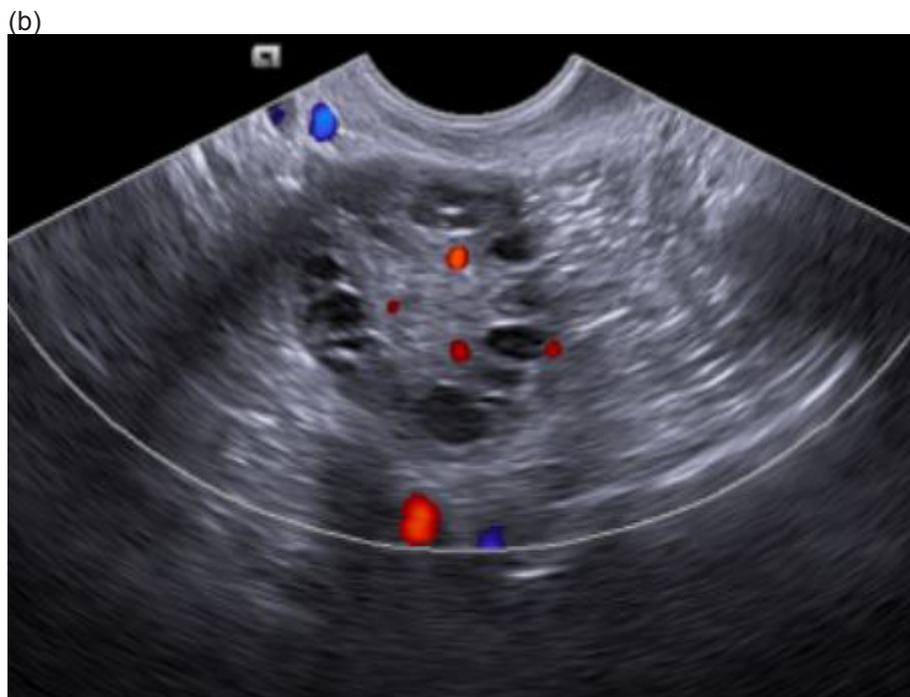
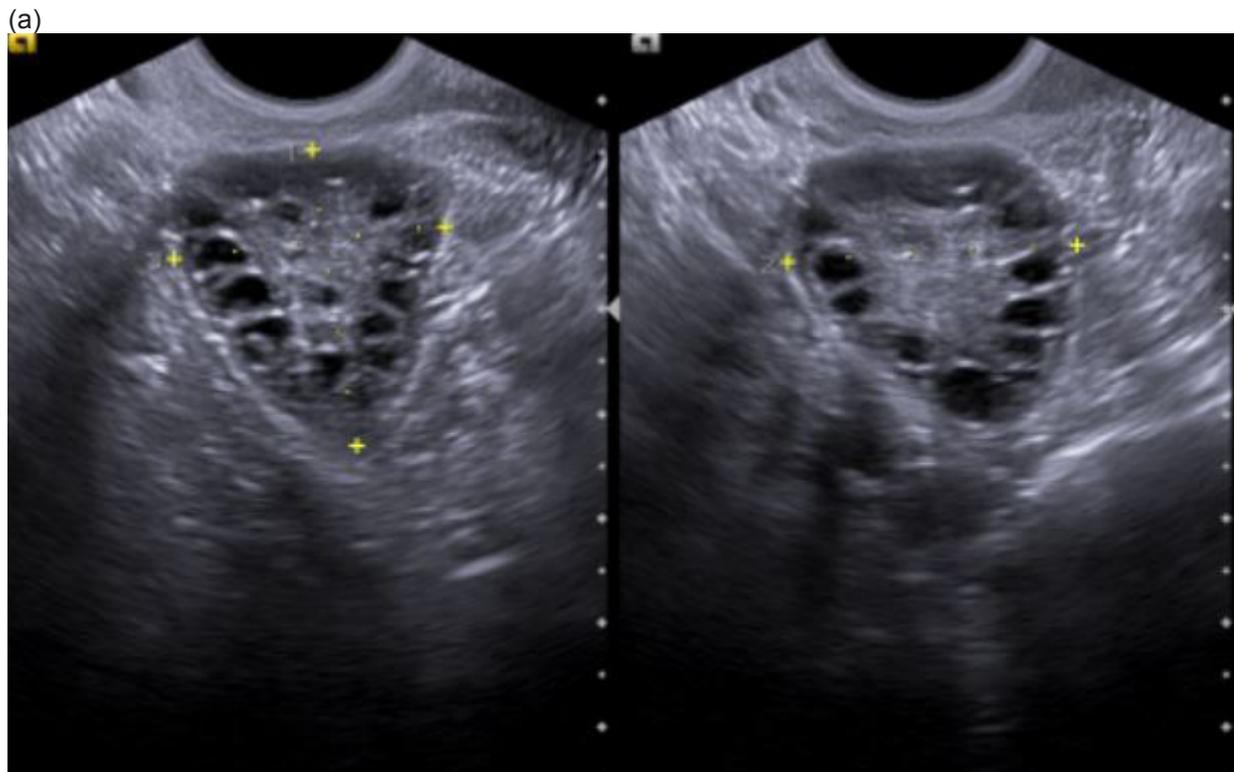


Figure (4): Ultrasound (a) and Doppler (b) of right ovary showing multiple peripheral small cysts with dense stroma.



Discussion

PCOS is an extremely common disorder occurring in 4-7% of reproductive age women with a widely variable prevalence among the different countries (range of 2.2% to 26%) as well as greatly depending on the population under assessment reaching 30% in women with secondary amenorrhea, 40% in women with infertility while it can be higher (75%) in cases of oligomenorrhea and can reach up to 90% in cases of hirsutism (1-9).

PCOS is known to be associated with reproductive morbidity and higher risk of endometrial cancer as well as increased risks of metabolic and cardiovascular disorders which is related to insulin resistance as well as an associated link with obesity. Women with PCOS are at higher risk for impaired glucose tolerance, diabetes mellitus type 2, hypertension, and cardiovascular disease, moreover some studies estimated a higher increased risk for myocardial infarction. Many lipid abnormalities are also noted. So early diagnosis of PCOS and close long-term follow-up and screening for diabetes and cardiovascular disease are warranted. Additionally, its therapy can improve the reproductive, metabolic, and cardiovascular risks (1, 4-8).

March et al (19) had conducted a cohort retrospective study for 728 women born during 1973–1975 in a single maternity hospital who were traced and interviewed in adulthood (age 27–34 year s). They described PCO prevalence using the criteria of the National Institutes of Health (NIH) and the advance criteria of Rotterdam and Androgen Excess Society (AES) (20). According to NIH criteria, the PCO prevalence was 8.7 + 2.0%, while the prevalence using the criteria of Rotterdam was 11.9 + 2.4% and increased to 17.8 + 2.8% after the addition of imputed data. The prevalence of PCO was 10.2 + 2.2% according to the AES criteria and increased to 12.0 + 2.4% after adding imputed data.

In another study conducted on Saudi females (29–43 years old), the prevalence was 64.5% in obese and 24.2% in overweight cases (21); in addition it suggested a high prevalence of obesity with infertility and PCOS (22-24). Another study conducted in South Australia found a PCO prevalence of 17.8% among 978 women (25) while Lau et al showed the PCOS prevalence of 12% among 100 women based on Rotterdam criteria (26). A higher prevalence of 69% was recorded in Khoury et al's ultrasound study (27) and this causes doubt in the use of ultrasound to diagnose PCOS (28).

Menstrual disorders, especially oligomenorrhea, can be a beginning to ovulatory dysfunction and infertility, and complications due to increased estrogens and androgens in later years, however complications can be reduced by early diagnosis of PCO (29).

The diagnosis of PCOS depends on a combination of one criteria from the following clinical criteria (include: hirsutism (with score of >8 according to the modified Ferriman and Gallwey) (30), menstrual cycle disturbance

(irregular; oligo- or amenorrhea), associated with one abnormal biological criteria (serum LH > 6.5 UI/l, and/or the levels of testosterone >0.7 ng/ml, and/or the levels of androstenedione > 2.2 ng/ml), or unilateral or bilateral volume of ovaries higher than 10 cm² measuring by ultrasound (31,32).

Pelvis ultrasound carries a major role in assessment of ovaries in cases of PCO, the sonographic diagnosis of PCO is demonstration of 12 or more follicles with a diameter of 2-9 mm, or increased ovarian volume > 10 cm³ (at least seen in one ovary).

If a follicle >10 mm is seen, then ultrasound should be repeated later for more accurate volume measurement. Classical sonographic PCO features are the peripheral follicular arrangement in the ovaries (string of pearls appearance) as well as increases ovarian stromal echogenicity (34,35).

It is important to avoid hormonal contraceptives during the ultrasound and hormonal assessment.

In our study, the prevalence of PCO was 6.85%, of which 75.6% was bilateral while 24.4 % was unilateral. Unilateral cases affected right ovary in 64.6 % while left ovary was the only one involved in 35.4%.

Cases with PCO at right ovary showed ovarian volume of more than 10 cc in 79%, follicles number of more than 12 in 81 %, dense stroma in 79.4% and peripheral follicular arrangement in 89.8%

Cases with PCO at left ovary showed ovarian volume of more than 10 cc in 75.3%, follicles number of more than 12 in 83 %, dense stroma in 76.7% and peripheral follicular arrangement in 88.6%

In PCO the growth of small ovarian follicles to become the dominant follicle is not occurring in a normal pattern (36). This is essential in the evaluating of anovulation in PCO, and this was shown to be higher in females with high blood insulin level as well as obese ladies (34).

There may be a misdiagnosis between PCO and other causes of multi-follicular ovaries (MFO) in which only the latest stages of follicular development (>4 mm) are involved. MFO can be seen

in some physiological and pathological conditions such as mid/late normal puberty, central precocious puberty, hypothalamic anovulation, hyperprolactinaemia. This diverted most of authors to assume 10 follicles as a threshold (35,37-38).

Transvaginal ultrasound (TVUS) is superior to transabdominal due to its higher resolution and no need for full urinary bladder as well as a more clear view of the internal structure of the ovaries, avoiding apparently homogeneous ovaries in obese women. In addition it is more time saving (39), so transvaginal scan is preferred especially with obese cases (38,41). A probe with >6.5

MHz is used in TVUS to have a good spatial resolution to obtain better results (42).

In another study (35) the prevalence of PCO was high (53.7%) and this was explained by higher incidence of obesity in that community.

Another study calculated stromal index (ratio of mean stromal echogenicity to mean echogenicity of the entire ovary) and total stromal echogenicity (43). There was no difference in the mean stromal echogenicity, however the stromal index in PCO women was significantly higher. The apparent subjective increase in stromal echogenicity in cases of polycystic ovaries as exemplified by the greater stromal index could be attributed to the combination of the increased ovarian stromal volume and significantly lower mean echogenicity of the entire ovary in such case., This reflects low sensitivity of ovarian echogenicity in the diagnosis of PCO.

Limitation of current study

Some cases were virgin, unmarried females thus transvaginal ultrasound could not be done.

Conclusion

The assessment of the ovaries has been greatly improved by sonographic diagnostic criteria of PCO. The diagnostic accuracy in addition to demonstration of ovarian size, can evaluate the characteristic patterns of follicles distribution and ovarian stromal changes. The presence of 12 or more follicles with 2–9 mm diameter is considered a good sensitive indicator more so than the ovarian volume or ovarian stromal increased echogenicity. Transvaginal ultrasound (TVUS) is considered the gold standard in the diagnosis of PCOS,

Ethical considerations:

The study is approved by PHCC institutional review board research.

Acknowledgement:

We wish to acknowledge the Primary Health Care Corporation (Qatar) as a research funding agency for this article.

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Venous Thromboembolism Awareness among Saudis Risk Group at Primary Health Care Centers in Riyadh

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Afaf Abdu Hakami et al. Venous Thromboembolism Awareness Among Saudi at Risk Groups at Primary Health Care Centers in Riyadh. World Family Medicine. June 2023; 21(5): 21-29

Abstract

Developing specialized health programs for the at-risk public begins with an assessment of knowledge. There is a lack of local research regarding at-risk groups' knowledge about venous thromboembolism. Our goal is to identify gaps in knowledge about VTE among communities at risk.

Methods: Quantitative cross-sectional study design was used. A questionnaire was administered to patients who were followed up in primary health care centers under Riyadh Second Health Cluster, and who were conveniently selected. Descriptive statistics were presented by using the Package for Social Sciences version 24 for statistical analysis.

Results: The results showed a total of 823 participants; 30% of them have lack of knowledge about DVT. Also, the majority of participants not aware about causes of a leg clot. More than half of the participants are not aware of PE and they did not report that chest pain, cough with blood, the heart rate becomes rapid as signs of PE. However, few of participants were worried about VTE and they agree that clots may result in death. Finally, the participants agreed that untreated blood clots in the leg cannot travel to the lungs.

Conclusion: To achieve the current Saudi Health Council evidence-based clinical practice guidelines, primary health care centers need to activate the role of health care providers. Future research should include a healthy Saudi general population. Educational programs regarding VTE could also be evaluated through interventional studies. The health care providers' perceptions of VTE and their role in raising awareness about VTE need to be assessed in practice.

Key words: Venous thromboembolism, awareness, risk groups, Saudi Arabia

Introduction

Venous thromboembolism (VTE) mainly relates to deep vein thrombosis (DVT) and pulmonary embolism (PE) which causes considerable morbidity and mortality. It strongly contributes to the global disease burden and negative consequences [1]. VTE is an outcome from an inequity of hemostasis and thrombosis [2]. In 2016, VTE was identified in over 1.2 million individuals in the United States (US) and 60% were diagnosed as DVT alone while 40% presented as pulmonary embolism with or without DVT [3].

It is important to note that VTE is a disease of complex nature that occurs within families. Genetic as well as acquired risk factors play an important role in its occurrence. It is important to recognize and manage high-risk individuals appropriately [4]. VTE risk assessment and prophylaxis constitute part of the preventive tools that can be utilized at health care providers' level. Therefore, reviewing whether VTE risk status has been established and administering approved VTE prophylaxis are accepted to be the central healthcare provider role [5]. Healthcare practitioners ought to identify patients at risk of developing VTE and select the appropriate therapy, thus reducing its incidence. In addition, to PE risk of death, DVT frequently results in a post-thrombotic syndrome that lowers quality of life [6]. Therefore, VTE prevention is an area that could be targeted to promote health and safety not only in healthcare settings, but also in the community. A population-based strategy would raise awareness of VTE and work to reduce lifestyle risk factors across the board through advocacy, policy changes, and environmental improvements [7].

In Malaysia, a deficit of knowledge regarding venous thromboembolism was reported among pregnant women's knowledge of venous thromboembolism [8]. In Nigeria, awareness and knowledge of the symptoms and risk factors of VTE was assessed among the general population. The majority of respondents correctly described DVT as a blood clot in the vein, but only few correctly described PE. Hospital stays, surgery, cancer, pregnancy, and old age were all known risk factors for VTE [9].

In the Saudi Arabia context, a study conducted to assess level of awareness among hospitalized patients in Saudi Arabia demonstrated lack of awareness of VTE, DVT, and PE among hospitalized patients [10]. Another study analyzed the awareness of VTE among Saudi Arabian adults by self-administered electronic questionnaire translated into Arabic. Around a third of the Saudi general population were unaware of DVT and PE [11]. However, about 60% of the respondents were aware of the symptoms of DVT and PE, indicating a positive attitude towards the knowledge of DVT and PE among the general public [11].

In Aseer, awareness of causes, risk factors, signs, symptoms, prevention, and treatment options toward VTE among the population was assessed [12]. Public awareness and knowledge regarding VTE is lacking,

and it is important to improve this awareness and knowledge in order to achieve better prevention of VTE [12]. Moreover, another study evaluated Saudi females' awareness of VTE symptoms and signs and their level of knowledge about the risk of VTE associated with oral contraceptive pills [13]. Female populations with diverse education levels, socioeconomic status, and background characteristics were asked to complete a structured online questionnaire. Among the 1,173 participants, 726 used or had previously used OCPs. Only 329 respondents (45%) and 303 respondents (41%) were aware of deep vein thrombosis (DVT) and pulmonary embolism (PE) as medical conditions, respectively, while 312 respondents (43%) were aware of the association between OCP use and DVT risk. There were 297 women who reported leg swelling as the primary symptom of DVT (40%), while 331 women reported shortness of breath as the primary symptom of PE (46%) [13].

In Makkah, Saudi Arabia, a study investigated hospitalized patients' awareness and perceptions of VTE and associated thromboprophylaxis. Between September and November 2021, 301 patients were recruited to participate in a descriptive cross-sectional study conducted at the Al-Noor Hospital's surgical ward. It was found that hospitalized patients were unaware of VTE, its clinical presentation, and its risk factors [14]. Furthermore, a related study surveyed 1,661 Saudis to evaluate the knowledge about DVT among western region residents [15]. There was prior awareness of DVT among approximately 45.5% of participants. A well-known risk factor is being overweight and traveling for long periods of time. In most of the participants (60%) who knew about DVT, pain and discomfort (97.8%) and leg pain (73.8%) were the most frequent clinical manifestations. Additionally, 45.3% of the participants were aware that DVT can be fatal, 36.4% were aware of more than one pulmonary embolism characteristic, 35% were aware of post-coagulation syndrome, and 12.6% were aware that pulmonary embolism is a serious condition. There were 12% who had a better understanding of DVT while 79% had a poor understanding [15].

Recently, a study investigated Saudi Arabians' knowledge and awareness of VTE [16]. 1226 Saudi adults (aged over 18 years) from the general population were asked to complete a validated online questionnaire. Most participants were unaware of VTE and were not concerned about it. However, there was a greater awareness of other medical conditions, such as hypertension [16]. A number of risk factors for VTE have been identified, including immobility and old age. Most participants correctly identified leg pain and tenderness as symptoms of deep venous thrombosis, despite less than half being aware of the association between thrombosis and VTE [16]. As symptoms of pulmonary embolism, most participants reported chest pain and breathlessness. The most commonly identified symptoms of VTE are leg paralysis and slow, shallow breathing. There was considerable disagreement among respondents regarding the statement "having a blood clot is not considered a medical emergency" [16].

This study aimed to assess VTE awareness among Saudi at risk groups at Primary Health Care Centers in Riyadh. While there is no local program exclusively for public health promotion addressing VTE prevention in Primary Health Care Centers with many known risk factors increasing in society such as cancer, immobility and obesity, VTE has a major impact on increasing public health problems which need to be focused on to avoid provoked VTE or recurrent VTE, through raising patient awareness of risk and symptoms, lifestyle counseling, and possibly statins or direct oral anticoagulants [7].

Furthermore, assessment of knowledge is a starting point to extract the needs of the public who are at risk and direct attention towards establishing specialized health programs for this group. If we can find gaps in knowledge of communities at risk regarding VTE, we can better educate them before they actually become patients. Also, it could help alleviate the economic burden on the health system of this common preventable condition. Nevertheless, there is lack of local investigation regarding knowledge and attitude of at-risk groups in primary health care settings.

Methodology

A quantitative cross-sectional study design was used. A questionnaire including 35 quotations was used to assess the public's awareness level about venous thromboembolism after obtaining permission [12].

This study was conducted in Primary Health Care Centers under Riyadh Second Health Cluster. There are five sectors under Cluster 2 and under each sector has 8 primary health care centers. Three sectors were selected randomly and a total of 13 primary health care centers were selected randomly from these sectors.

Populations and sampling were patient follow up in primary health care centers under Riyadh Second Health Cluster. A convenience sampling was applied and every patient visiting maternity and chronic disease clinics had a chance to participate in the study. The inclusion criteria were all patients and their family members visiting maternity and chronic disease clinic primary health care centers. Exclusion criteria were patients under 18 years old and patients who were followed up in the dental or emergency clinic. Descriptive statistics were presented by using The Statistical Package for Social Science version 24 for statistical analysis. IRB approval was obtained from King Fahad Medical City Log # (22-337E).

Results

A total of 823 participants participated in this study. Half of the participants were between 18 -39 years old and female. Regarding the educational level 38.9 held a university degree. The majority of the participants had medical conditions such as asthma, obesity, colon and anemia. In addition, more than half had diabetic and hypertension conditions. Also, the majority of females were pregnant (Table 1).

The results showed that more than one third of the participants were not aware about DVT. On the other hand, more than half of participants had awareness about heart attack, thrombosis, stroke, and the majority were aware about elevated blood pressure (Table 2). More than half of the participants did not know what a leg clot and its causes were. Moreover, the majority didn't perceive that a tumor in a vein, lack of oxygen in the vein, blood stasis in vein are causes of DVT. Additionally, the majority of participants reported that leg pain, a noticeable change in the color of your leg, fever in the leg, leg paralysis, swelling in your leg are not signs of DVT (Table 3).

Regarding awareness of PE more than half of the participants are not aware of PE. Additionally, they did not report that chest pain, cough with blood, the heart rate becomes rapid are signs of PE. However, only (58.1%) indicated that slow, shallow breathing and (49%) headache are signs of PE (Table 4). Also, the majority did not indicate that high blood pressure, blood donation, having a family member with history, being over 65 years of age, cancer, being immobile for a long period of time, pregnancy or after childbirth, a hospital stay and surgeries are risks for developing blood clot but they agreed that this health problem can be treated by medications. However, more than half of the participants don't rely on health care providers as a source of information about VTE. However, relying on other sources such as the internet, television or friends was lower than depending on specialists as a source of information (Table 5).

Only less than half of participants were worried about coagulation, brain attack, leg embolism (deep vein thrombosis), pulmonary artery embolism (lung embolism) and more than half were worried about heart attack and hypertension (Figure 1). Finally, there is a disagreement among participants that untreated blood clots in the leg cannot travel to the lungs and a blood clot is not considered an emergency. Moreover, they agree that clots may result in death (Figure 2).

Characteristics		Frequency	%
Age	18-39 years	406	49.3
	40-65 years	317	38.5
	More than 65 years	100	12.2
Gender	Male	350	42.5
	Female	473	57.5
Educational Level	Primary	52	6.3
	Intermediate	84	10.2
	Secondary	236	28.7
	University	320	38.9
	Master	14	1.7
	Uneducated	117	14.2
Health Status	High blood pressure	477	58.0
	Diabetes	478	58.1
	Asthma	674	81.9
	Obesity	822	99.9
	Colon	822	99.9
	Anemia	821	99.8
	Pregnant	791	96.1

Table 2: Awareness of DVT

	NO		YES	
	Frequency	%	Frequency	%
Do you know or have you ever heard about Heart attack?	86	10.7	716	89.3
Do you know or have you ever heard about Thrombosis?	183	22.8	619	77.2
Do you know or have you ever heard about Stroke?	240	29.9	562	70.1
Do you know or have you ever heard about Leg stroke (deep vein thrombosis)?	381	47.5	421	52.5
Do you know or have you ever heard about Pulmonary embolism?	380	47.4	422	52.6
Do you know or have you ever heard about High blood pressure?	36	4.5	766	95.5

Table 3: Awareness of DVT Causes and Symptoms

Items	NO		YES	
	Frequency	%	Frequency	%
Do you know what is the meaning of a clot in the leg and how do you feel if you get it?	501	62.5	301	37.5
Which of the following statements do you think describes the cause of deep vein thrombosis (leg thrombosis):				
Tumor in a vein	680	84.8	122	15.2
Lack of oxygen in the vein.	653	81.4	149	18.6
Blood stopped in vein	515	64.2	287	35.8
I'm not sure	435	54.2	367	45.8
Identify the signs and symptoms of a blood clot in your leg (deep vein thrombosis):				
Leg pain	507	63.2	295	36.8
A noticeable change in the color of your leg	669	83.4	133	16.6
Fever in the leg	681	84.9	121	15.1
Leg paralysis	690	86.0	112	14.0
Swelling in your leg	490	61.1	312	38.9

Table 4: Awareness of PE

Statements	NO		YES	
	Frequency	%	Frequency	%
Do you know what is the meaning of a blood clot in the lung (pulmonary embolism), and how you would feel if you had one?	548	68.3	254	31.7
Identify signs and symptoms of a blood clot in your lung (pulmonary embolism).				
Pain spreading to the arm	691	86.2	111	13.8
Frequent headaches *	753	93.9	49	6.1
Chest pain	413	51.5	389	48.5
Cough with blood	727	90.6	75	9.4
The heart rate becomes rapid	675	84.2	127	15.8
Slow, shallow breathing *	336	41.9	466	58.1
Shortness of breathing	370	45	453	55

* Incorrect answer

Table 5: Awareness of Blood Clot

Which of the following could increase your risk of blood clots?	NO		YES	
	Frequency	%	Frequency	%
High blood pressure	696	86.8	106	13.2
High cholesterol *	802	100.0	0	0
Donate blood	802	100.0	0	0
Having a family member	741	92.4	61	7.6
Being over 65 years of age	657	81.9	145	18.1
Excessive exercise *	799	99.6	3	.4
Cancer	778	97.0	24	3.0
Being immobile for a long period of time	630	78.6	172	21.4
Pregnancy or after childbirth	742	92.5	60	7.5
A hospital stay	734	91.5	68	8.5
Surgeries	700	87.3	102	12.7
In your opinion, what is the treatment usually used to treat blood clots?				
Medications	244	30.4	558	69.6
Surgeries	584	72.8	218	27.2
Herbal Therapy	776	96.8	26	3.2
What source of information do you rely on for information about coagulation?				
Specialist	454	56.6	348	43.4
Internet	507	63.2	295	36.8
Television	701	87.4	101	12.6
A friend	744	92.8	58	7.2

* Incorrect answer

Figure 1: How concerned are you about each of these health conditions

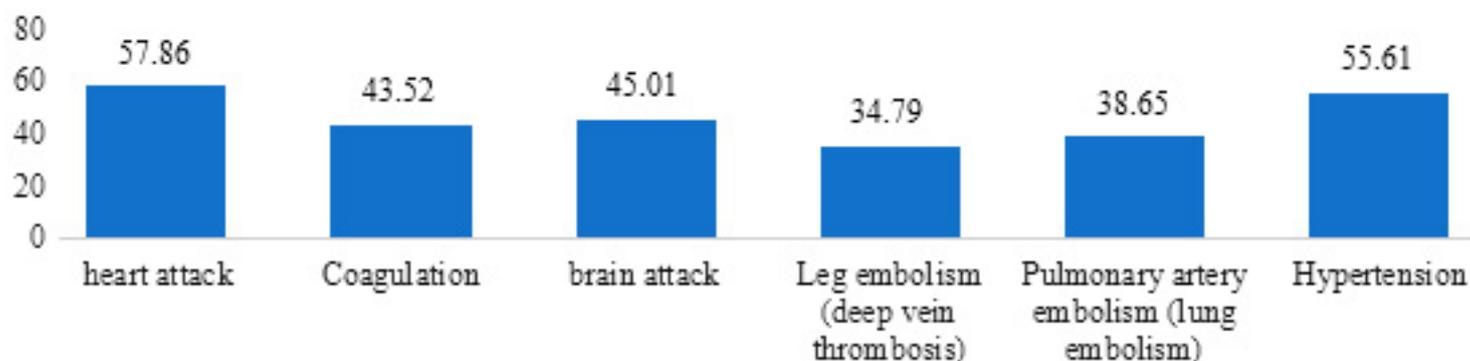
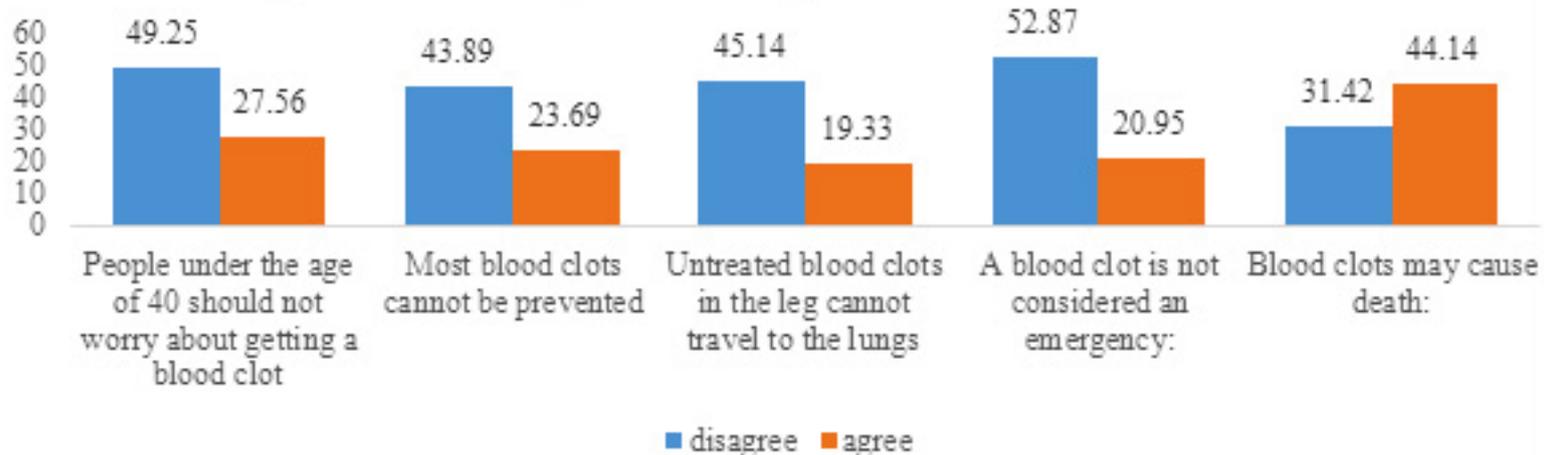


Figure 2: Participants Perception related to blood clots



Discussion

Results of the current study indicated that the risk group population were not aware about DVT. On the other hand, they were aware about medical conditions such as; heart attack, thrombosis, stroke, and the majority were aware about elevated blood pressure. This goes consistently with a study in Riyadh where DVT was known by 18% of participants only [17]. On the other hand, the majority of patients and caregivers reported awareness about DVT among the population in the Aseer Region [12]. Additionally, it was reported that 45% of the general population living in the Western region of Saudi Arabia were aware of DVT [15]. However, there was a greater awareness regarding medical conditions such as elevated blood pressure [16].

The current study reported that the risk group participants did not know what a leg clot and its causes were. Moreover, the majority didn't perceive that tumor in a vein, lack of oxygen in the vein, blood stasis in vein are causes for DVT. The most frequently defined risk factors were immobility or bed rest for longer than 3 days, trauma, long airline travel, cancer and being overweight [12][15].

Additionally, the majority of participants in the current study reported that leg pain, a noticeable change in the color of your leg, fever in the leg, leg paralysis, swelling in your leg are not signs of DVT. Other studies reported that calf pain, swelling, redness, and discomfort of the legs, skin color changes and fever were the most known signs [12][15]. On the other hand, leg paralysis and itching were indicated as signs of DVT [17]. Regarding awareness of PE, participants in the current study were not aware of PE. This result is consistent with studies indicating that only 38.7% and 12.6% were aware of pulmonary embolism [17] [15].

Additionally, the risk group participants indicated that slow, shallow breathing is a sign of PE. On the other hand, the majority did not indicate the risks for developing blood clot but they agreed that this health problem can be treated by medications. Shortness of breath and chest pain were the most recognized symptoms of PE [17]. However, in another study, 36.4% of participants identified more than one sign of PE, though 45.8% did not know any sign[15].

Also, the majority did not indicate that high blood pressure, high cholesterol, blood donation, having a family member with a history, being over 65 years of age, excessive exercise, cancer, being immobile for a long period of time, pregnancy or after childbirth, a hospital stay and surgeries are risks for developing blood clot but they agreed that this health problem can be treated by medications. By contrast, hospital stays, surgery, cancer, pregnancy, and old age, obesity, traveling and immobile were indicated as risk factors [8][15][16]. Moreover, it was reported that women were aware of the relationship between OCP and DVT [13].

In this study, most participants indicated that they don't rely on health care providers as a source of information about VTE. However, relying on other sources such as the internet, television or friends was lower than depending on specialists as a source of information. A relevant study reported, 38.1% rely on sources such as social media, the internet, scientific books, and study in gaining knowledge regarding DVT [15]. An important aspect of primary health care center's activities is educational programs and awareness promotion campaigns. On the other hand, the health information regarding VTE is most commonly obtained from doctors or healthcare professionals [11]. Moreover, since VTE accounts for a significant healthcare burden with many cases being undetected, it is critical to raise awareness about its symptoms and associated clinical presentations among the general public so that it can be diagnosed early and managed appropriately [18].

Finally, there is a disagreement among participants that untreated blood clots in the leg cannot travel to the lungs and a blood clot is not considered an emergency. Moreover, they agree that clots may result in death which is consistent with the result that more than one third indicated that DVT led to mortality and a few considered pulmonary embolism a serious condition [15].

Implications

For community health it will be valuable to activate the health awareness programs about VTE among the public in general and those who are at risk in particular since there is a health initiative to enhance awareness during the month of March every year.

For future research, it is recommended to expand the sample to involve a healthy general population in Saudi Arabia. Also, interventional studies could be conducted to determine the effect of educational programs regarding VTE.

For practice, there is a need to assess the health care providers' perceptions regarding VTE and identify patients who are at risk and their role in enhancing awareness.

Limitations

The main limitation in this study is the research design because bias can occur in cross sectional surveys. Another limitation was that the population and sample size in primary health care centers is difficult to be accurate because of a lack of data and source of data.

Conclusion

VTE awareness is underestimated and there is a need to enhance awareness among people who are at risk. Additionally, there is a need to activate the role of health care providers in primary health care centers to apply the current evidence based clinical practice guidelines that were developed by the Saudi Health Council.

Acknowledgements

The authors thanks Al Bshabshe, A. for his contribution and giving permission to use their developed tool to accomplish this study.

Funding Statement and Declaration of Interests

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statement:

Authors declare no financial support or relationships that may pose conflict of interest.

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Prevalence of Colonic Diverticulosis among Adult patients with Obesity and metabolic syndrome conditions, a Retrospective Study at a University Hospital in Saudi Arabia

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Hani Jawa et al. Prevalence of Colonic Diverticulosis among Adult patients with Obesity and metabolic syndrome conditions, a Retrospective Study at a University Hospital in Saudi Arabia. World Family Medicine. June 2023; 21(5): 30-36 DOI: 10.5742/MEWFM.2023.95256108

Abstract

Background: Obesity is a common health problem that restricts people's daily activities. Many observational studies found that diverticulosis is a common complication for obesity and the prevalence of diverticulosis is increasing. However, the correlation between obesity and diverticulosis remains controversial.

Aim: The primary aim of our study was to assess the prevalence and the association between overweight or obesity and the rate of diverticulitis (as diagnosed by CT scans).

Methods: Our study was based on reviewing the medical records in a single medical center in Saudi Arabia over a period of 3 years. 342 patients diagnosed with diverticulosis and confirmed by colonoscopy and CT scan were included, with those ages above 18 years old receiving a health examination, measurement of percentage of body fat, blood test and colonoscopy at King Abdulaziz University.

Results: Women with body mass index (BMI \geq 30) had a greater risk of developing diverticulosis (PR, 1.58; 95% CI, 1.05–2.06) when compared to women with normal BMI. By gender, in patients less than fifty-one, occurrence of colonic diverticulosis was less in female patients compared to males (29% vs 45%, $P=0.06$). However, in older ages there wasn't clear difference among male and female patients in the prevalence of diverticulosis.

Conclusion: 342 patients who underwent screening colonoscopies for diverticulosis, were included in our analysis. We found that the risk of colonic diverticulosis has an obvious correlation to obesity especially in women with BMI \geq 30. When comparing by age, colonic diverticulosis was less predominant in premenopausal-age women compared with similar-age men. These findings may be due to female sex hormones that enhance diverticulosis development.

Key words: colonic diverticulosis, obesity, metabolic syndrome, Saudi Arabia

Introduction

Diverticula are structural alterations within the colonic wall. Diverticulosis are structural alterations within the colonic wall that form "pockets". Diverticulosis forms from herniation of the colonic mucosa and sub-mucosa through defects in the circular muscle layers within the colonic wall, often at the sites of penetrating blood vessels in the colon(1). Diverticulosis is common in older adults, occurring in 50% of individuals aged 60 years. The prevalence of diverticulosis in Western and industrialized countries (eg, United States, Europe) is higher than countries such as Africa and Asia, which have prevalence rates of less than 0.5% (2, 3). The prevalence has reached seventy five percent among patients aged above eighty years old (4, 5). Although most cases of diverticulosis have no symptoms, some may proceed to significant consequences that include acute diverticulitis, colonic bleeding, and perforation(6).

Many modifiable risk factors may predispose to diverticulosis such as, decreased intake of fibers and vegetables, increased intake of fat and meat, decreased physical exercise, and smoking. The prevalence of diverticulosis is higher in old age than in young age, which is thought to be the most effective risk factor (7, 8). One quarter of symptomatic cases develop diverticular bleeding or diverticulitis, and a small minority will become complicated by bowel obstruction or abscess formation. The majority of symptomatic cases appear with colicky stomach pain without inflammation(9). Obesity is defined when BMI is equal to or above 30 kg/m² and it is clearly increasing all over the world(10). Obesity is linked to several disabling comorbid conditions, such as cancer, metabolic syndrome, osteoarthritis, ischemic heart disease, hypertension, diabetes mellitus, gastro-esophageal reflux, obstructive sleep apnea and certain cancers (11).

It's known that understanding adaptable risk factors for colonic diverticulosis may help avoid diverticular illness and advance our knowledge of the biology of the condition. However, information is limited addressing any potential links between overweight and diverticulitis and its severity as well as obesity along with the severity of developing diverticulosis in males and females. We aim in our study to assess the relation between obesity and the risk of colonic diverticulosis using data from a department of internal medicine at King Abdulaziz University, Jeddah, of cohorts seeking to do screening colonoscopy and thorough checkup for diverticulosis.

Methods

In our study, we depended on a retrospective review of saved medical records between January 2015 until December 2019 at the Department of Internal Medicine at King Abdulaziz University, Jeddah. Ethical approval was taken from the University of King Abdulaziz. Adult cohorts whose age was more than 18 years old and who had a confirmed diagnosis of diverticulosis were included. On the other hand, patients with colorectal cancer, presence of inflammatory bowel illness, a history of previous colorectal surgery, and the absence of a confirmation colonoscopy after diverticulitis were excluded.

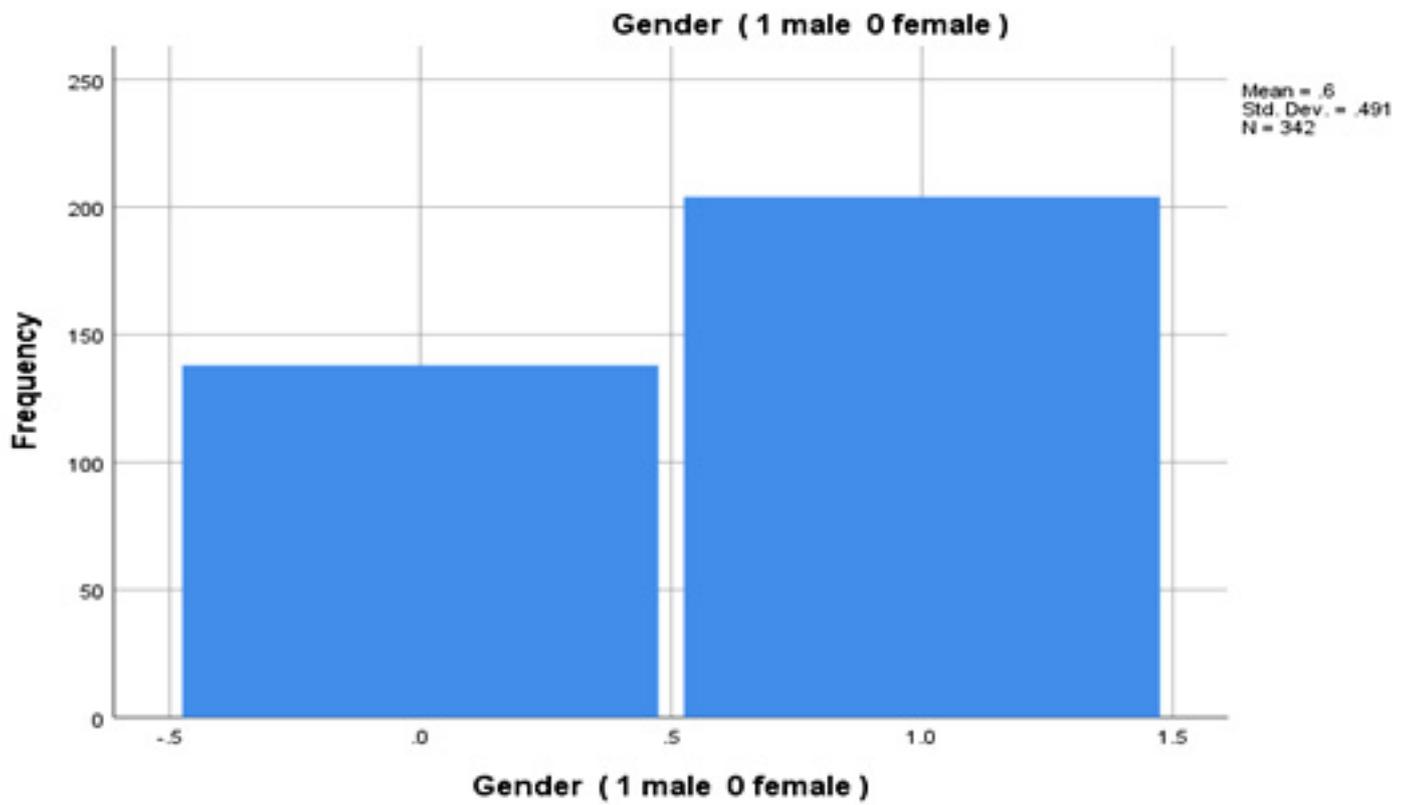
To confirm clinical presentation and complaints, all patient data, including demographic information, height, and weight upon admission, was checked. Additionally, if present, any additional comorbidities were noted (such as diabetes, hypertension, or dyslipidemia). The WHO formula (BMI equals mass in kilograms divided by the square of height in meters) was used to calculate BMI for each case. We used the WHO classification for obesity in each case. In patients whose BMI ranged from 18.5 to 24.9 kg/m² it was defined as normal, and overweight where their BMI ranged from 25 to 29.9 kg/m², and obese if their BMI was equal or above 30 kg/m²(12). Colonoscopy and radiological findings were recorded.

Statistical analysis was defined using one way analysis of variable quantity testing. A p-value when less than 0.05 was thought to be significant. We used logistic regression to find the relation between total body fat and diverticulosis. Descriptive statistics and Student's t test were used with alpha set at $p < .05$. We performed multivariate analyses through modified Poisson regression to measure the prevalence ratios and 95% CIs. All analyses were stratified by gender.

Results

We included 342 patients in our analysis of whom, 40.35% were women and 59.65% were men (Figure 1).

Figure 1



The mean age was 63.46 and SD (12.784) (Table 1). It was noticed that the incidence of diverticulosis increases with age as seen in Figure 3. In patients aged less than 51 we found that the prevalence of diverticulosis was more in men compared to women. Right colonic diverticulosis was more prevalent in women (17%) compared to men (7%) while left and bilateral colonic diverticulosis was more prevalent in male patients (57.2%) compared to women (53.9%). On the other hand, in patients whose age ranged from 51 to 60, the occurrence of diverticulosis was more in females than males (37% and in men 43%). For patients over the age of 60 the incidence was equal in both genders as follows, (females 55% and males 57%). Comparing female patients with and without diverticulosis, diverticulosis was more prominent in older patients. The majority of the patients weren't from Saudi (66.08%) as seen in Table 1, Figure 2.

Table 1: Main indication for colonoscopy among male patients with diverticulosis

	Male		Female	
	No. of cases (% of total)	Total (201)	No. of cases (% of total)	Total (201)
Age	56.3 ± 6.8		54.7 ± 7.4	
Abdominal pain	23(11.4%)	201	33(16.3%)	141
Anemia	22(10.9%)	201	22(15.6%)	141
Hematochezia	32(15.9%)	201	16(11.3%)	141
Constipation	8(4%)	201	3(2.1%)	141
Diarrhea	2(1%)	201	4(2.8%)	141
Weight loss	3(1.5%)	201	2(1.4%)	141
Crohn's disease	2(1%)	201	1(0.7%)	141
Ulcerative colitis	3(1.5%)	201	1(0.7%)	141
Screening	78(38.8%)	201	65(46.1%)	141
Surveillance	14(7%)	201	6(4.3%)	141
Abnormal imaging	7(3.5%)	201	2(1.4%)	141
Right sided diverticulosis	14 (7%)	201	24(17%)	141
Left sided diverticulosis	115(57.2%)	201	76(53.9%)	141
Bilateral diverticulosis	54(26.9%)	201	32(22.7%)	141
Diabetes	87(43.3%)	201	61(43.3%)	141
Dyslipidemia	36(17.9%)	201	33(23.4%)	141
HTN	99(49.3%)	201	80(56.7%)	141
Saudi	131(65.2%)	201	95(67.4%)	141

Figure 2

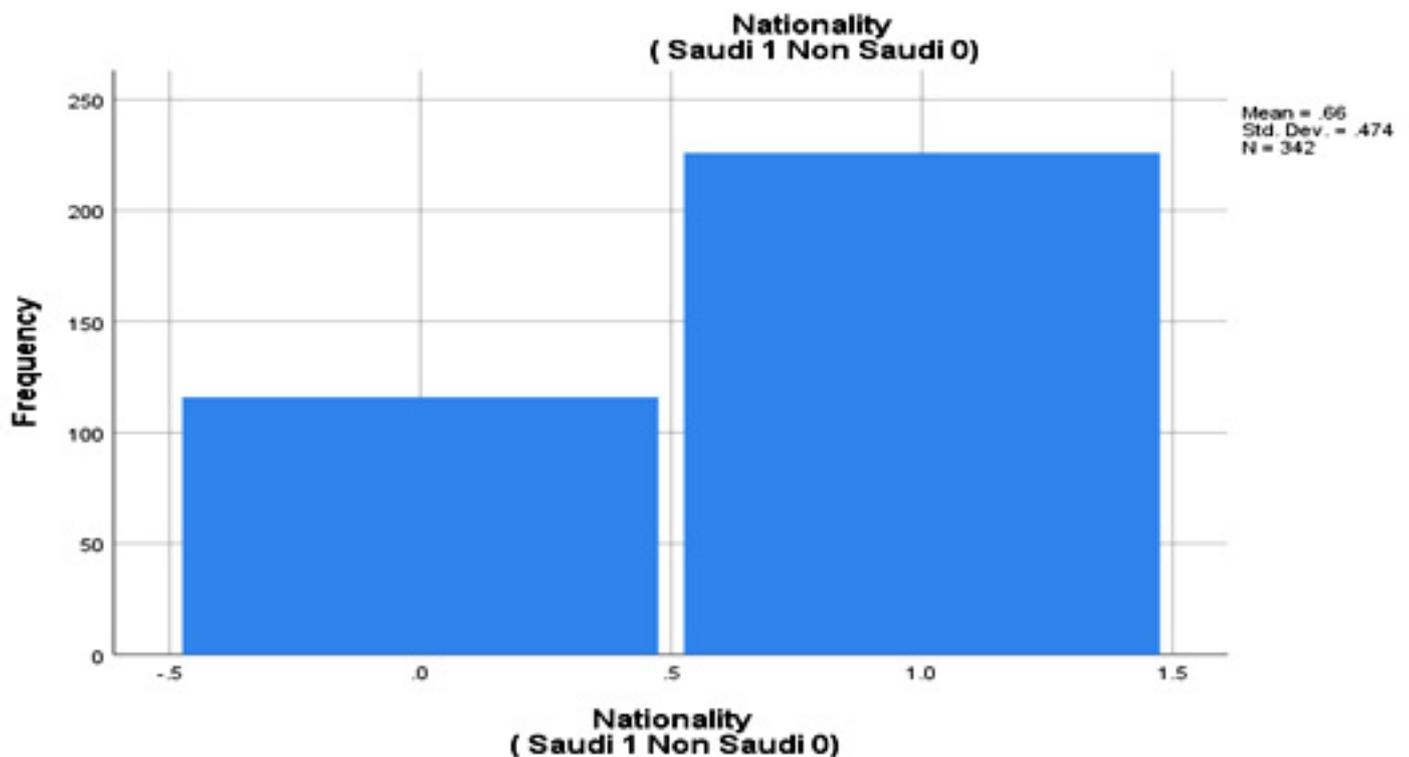
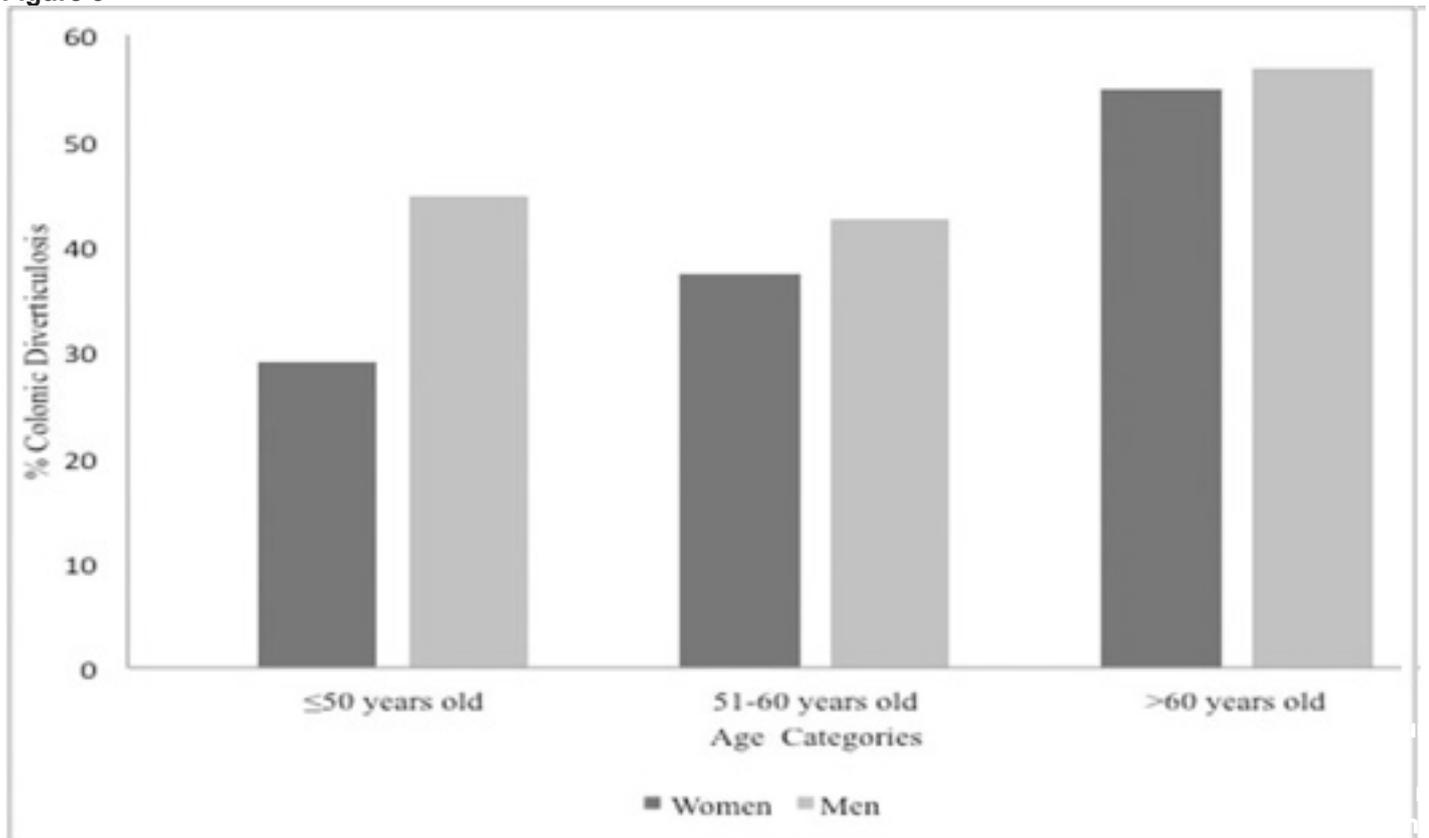


Figure 3



After taking confounding variables into consideration, diverticulosis was more prevalent in obese women (BMI ≥ 30) compared to women with normal BMI as following, (PR 1.48; 95% CI 1.08–2.04) (Table 2). There was no link between BMI and risk of diverticulosis among patients more than fifty years old.

Table 2

	Body mass index, kg/m ²			P-value
	18–25	25–30	>30	
Cases (n)	36	33	63	
Prevalence ratios (95% CI)	1.0	1.28 (0.84, 2.00)	1.59 (1.12, 2.18)	0.005
Adjusted prevalence ratios (95% CI)	1.0	1.23 (0.58, 1.55)	1.46 (1.05, 2.02)	0.02

Discussion

In our retrospective cohort study, we found that premenopausal women appear to be more resistant to diverticulosis than men of the same age, and that there was no difference in diverticulosis rates between the sexes after the age of fifty. Obesity, as determined solely by body mass index, has previously been established to be a risk factor for diverticulosis in Western populations(13-15). In contrast to earlier research, the current study used colonoscopy to ascertain if participants had colonic diverticulosis, investigated the relationship between diverticulosis and a number of obesity-related measures, and considered the impact of sex on these relationships. Similar to our findings, a German and Lithuanian genetic investigation of colonic diverticulosis discovered that obesity was linked to a higher incidence of diverticulosis in females than in males (16).

Women compared to men were considerably more at risk for colonic diverticulosis due to general obesity, not central obesity. Only younger-aged women were at a greater risk. Premenopausal women who are obese have greater levels of free testosterone and lower levels of total estrogen and sex hormone-binding globulin (17). We propose that premenopausal ovarian hormones containing steroids may guard against diverticulosis in females. Obesity during premenopause may raise the risk by raising free testosterone and lowering circulating estrogen. Although changes in the gut microbiome are linked to obesity, a previous study revealed little correlation among colonic diverticulosis and the makeup of the mucosal adherent microbial species (18). Other evidence opposing the idea that constipation is the main factor contributing to diverticulosis is the fact that men are more likely than women to report having looser and more frequent bowel movements (19). Colonic diverticulosis is more common in women than in males, which would be expected if the notion that it develops from constipation and increased intraluminal pressures is accurate (20, 21) although the link between sex and diverticulosis is still unclear in past studies(22). A study done on Japanese patients found that there was a major association between male patients and diverticulosis in multi-variate assessments(23). Though, in a study on Korean cohorts, reported that there was no link between sex and diverticulosis. In keeping with earlier research in Taiwan, we also discovered that participants who were elder were more probable than younger subjects to have diverticulosis(24, 25).

This study has many limitations. We would anticipate uniform changes in waist measures because each participant was prepared for the treatment. This would be a bias in measurement away from the null that is non-differential. Colonic diverticulosis may have been missed despite a thorough colonoscopy done by a qualified gastroenterologist with a trained research assistant present to record anthropometric measurements before the colonoscopy. Therefore, we were unable to determine whether obesity during infancy or weight gain over time is related to diverticulosis. Furthermore, as this was a cross-

sectional study, relationships were investigated rather than causality.

To conclude, women who were obese had a considerably higher chance of developing colonic diverticulosis. Diverticulosis in men did not correlate with any measure of obesity. Compared to males of similar ages, women in the premenopausal stage of life had a lower prevalence of diverticulosis. These gender disparities might have repercussions that help us understand the pathophysiology of diverticulosis.

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Acute painful crises may be causes of sudden deaths in sickle cell diseases

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Helvacı M R et al. Acute painful crises may be causes of sudden deaths in sickle cell diseases. World Family Medicine. June 2023; 21(5): 37-49 DOI: 10.5742/MEWFM.2023.95256109

Abstract

Background: Sickle cell diseases (SCDs) are severe inflammatory processes on vascular endothelium, especially at the capillary level because the capillary system is the actual distributor of hardened red blood cells (RBCs) into the tissues.

Methods: All cases with the SCDs were included.

Results: We studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p>0.05$, respectively). Disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), cirrhosis (8.1% vs 1.8%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), digital clubbing (14.8% vs 6.6%, $p<0.001$), coronary heart disease (18.0% vs 13.2%, $p<0.05$), chronic renal disease (9.9% vs 6.1%, $p<0.05$), chronic obstructive pulmonary disease (25.2% vs 7.0%, $p<0.001$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher in males but not acute chest syndrome (2.7% vs 3.7%), pulmonary hypertension (12.6% vs 11.7%), deep venous thrombosis and/or varices and/or telangiectasias (9.0% vs 6.6%), or mean age of mortality (30.2 vs 33.3 years) ($p>0.05$ for all).

Conclusion: The hardened RBCs-induced capillary endothelial damage, inflammation, edema, and fibrosis are initiated at birth, and terminate with disseminated tissue hypoxia and multiorgan failures even at childhood in the SCDs. Although RBCs supports and corticosteroids in acute phase and aspirin plus hydroxyurea both in acute and chronic phases decrease severity of the diseases, survivals are still shortened in both genders, dramatically. Infections, medical or surgical emergencies, or emotional stresses-induced increased basal metabolic rate aggravates the sickling and capillary endothelial edema, and may terminate with acute painful crises, multiorgan failures, and sudden deaths.

Key words: Sickle cell diseases, acute painful crises, sudden deaths, capillary endothelial inflammation, capillary endothelial edema, atherosclerosis, aging

Introduction

Chronic endothelial damage may be the chief cause of aging and death by causing end-organ failures in human being (1). Much higher blood pressures (BPs) of the afferent vasculature may be the main accelerating factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly affected in the destructive process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures, those eventually reduce blood supply to the terminal organs, and increase systolic and decrease diastolic BPs further. Some of the well-known accelerating factors of the destructive process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheral artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, aging, and dementia-like end-organ insufficiencies, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the destructive process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome, extensively (4-6). On the other hand, sickle cell diseases (SCDs) are chronic inflammatory and highly destructive processes on vascular endothelium, initiated at birth and terminated with an advanced atherosclerosis-induced end-organ insufficiencies in much earlier ages (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the main problem since sickling is rare in peripheral blood samples of the patients with associated thalassemia minors (TMs), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present in whole lifespan, but exaggerated with inflammations, infections, and additional stresses of the body. The hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia in whole body (9). As a difference from other causes of chronic endothelial damage, SCDs keep vascular endothelium especially at the capillary level (10, 11) because the capillary system is the actual distributor of the hardened RBCs into the tissues. The hardened RBCs-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages. Vascular narrowings and occlusions-induced tissue ischemia and end-organ insufficiencies are the terminal consequences, so the life expectancy is decreased by 25 to 30 years for both genders in the SCDs (8).

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All cases with the SCDs were included. The SCDs are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, acute painful crises per year, transfused units of RBCs in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure systolic BPs of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (12). Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, since the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BPs of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of higher than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with

the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p>0.05$, respectively). Prevalences of associated TMs were similar in both genders, too (72.5% vs 67.9%, $p>0.05$, respectively). Smoking (23.8% vs 6.1%) and alcohol

(4.9% vs 0.4%) were higher in males ($p<0.001$ for both) (Table 1). Transfused units of RBCs in their lives (48.1 vs 28.5, $p=0.000$), disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), cirrhosis (8.1% vs 1.8%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), digital clubbing (14.8% vs 6.6%, $p<0.001$), CHD (18.0% vs 13.2%, $p<0.05$), CRD (9.9% vs 6.1%, $p<0.05$), COPD (25.2% vs 7.0%, $p<0.001$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher in males but not ACS (2.7% vs 3.7%), PHT (12.6% vs 11.7%), DVT and/or varices and/or telangiectasias (9.0% vs 6.6%), or mean age of mortality (30.2 vs 33.3 years) ($p>0.05$ for all) (Table 2). Beside that the mean ages of terminal consequences were shown in Table 3.

Table 1: Characteristic features of the study patients

Variables	Male cases with SCDs*	p-value	Female cases with SCDs
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated TMs‡	72.5% (161)	Ns	67.9% (144)
<u>Smoking</u>	<u>23.8% (53)</u>	<u><0.001</u>	<u>6.1% (13)</u>
<u>Alcoholism</u>	<u>4.9% (11)</u>	<u><0.001</u>	<u>0.4% (1)</u>

*Sickle cell diseases †Nonsignificant ($p>0.05$) ‡Thalassemia minor

Table 2: Associated pathologies of the study patients

Variables	Male cases with SCDs*	p-value	Female cases with SCDs
Painful crises per year	5.0 ± 7.1 (0-36)	Ns†	4.9 ± 8.6 (0-52)
<u>Transfused units of RBCs‡</u>	<u>48.1 ± 61.8 (0-434)</u>	<u>0.000</u>	<u>28.5 ± 35.8 (0-206)</u>
<u>Disseminated teeth losses (<20 teeth present)</u>	<u>5.4% (12)</u>	<u><0.001</u>	<u>1.4% (3)</u>
<u>COPD§</u>	<u>25.2% (56)</u>	<u><0.001</u>	<u>7.0% (15)</u>
<u>Ileus</u>	<u>7.2% (16)</u>	<u><0.001</u>	<u>1.4% (3)</u>
<u>Cirrhosis</u>	<u>8.1% (18)</u>	<u><0.001</u>	<u>1.8% (4)</u>
<u>Leg ulcers</u>	<u>19.8% (44)</u>	<u><0.001</u>	<u>7.0% (15)</u>
<u>Digital clubbing</u>	<u>14.8% (33)</u>	<u><0.001</u>	<u>6.6% (14)</u>
<u>CHD¶</u>	<u>18.0% (40)</u>	<u><0.05</u>	<u>13.2% (28)</u>
<u>CRD**</u>	<u>9.9% (22)</u>	<u><0.05</u>	<u>6.1% (13)</u>
<u>Stroke</u>	<u>12.1% (27)</u>	<u><0.05</u>	<u>7.5% (16)</u>
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
ACS*****	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ± 8.4 (19-50)	Ns	33.3 ± 9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis *****Acute chest syndrome

Table 3: Mean ages of the consequences of the sickle cell diseases

Variables	Mean age (year)
Ileus	29.8 ± 9.8 (18-53)
Hepatomegaly	30.2 ± 9.5 (5-59)
ACS*	30.3 ± 10.0 (5-59)
Sickle cell retinopathy	31.5 ± 10.8 (21-46)
Rheumatic heart disease	31.9 ± 8.4 (20-49)
Autosplenectomy	32.5 ± 9.5 (15-59)
Disseminated teeth losses (<20 teeth present)	32.6 ± 12.7 (11-58)
Avascular necrosis of bones	32.8 ± 9.8 (13-58)
Epilepsy	33.2 ± 11.6 (18-54)
Priapism	33.4 ± 7.9 (18-51)
Left lobe hypertrophy of the liver	33.4 ± 10.7 (19-56)
Stroke	33.5 ± 11.9 (9-58)
COPD†	33.6 ± 9.2 (13-58)
PHT‡	34.0 ± 10.0 (18-56)
Leg ulcers	35.3 ± 8.8 (17-58)
Digital clubbing	35.4 ± 10.7 (18-56)
CHD§	35.7 ± 10.8 (17-59)
DVT¶ and/or varices and/or telangiectasias	37.0 ± 8.4 (17-50)
Cirrhosis	37.0 ± 11.5 (19-56)
CRD**	39.4 ± 9.7 (19-59)

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stresses are the most common precipitating factors of the crises (19). The increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan insufficiencies. So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelae on the capillary endothelial system all over the body. After a period of time, the sequelae may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of them are cases without hydroxyurea therapy (20, 21). Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in terminal cases due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means

of the blood subgroup mismatch. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs (20, 21). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (20, 22). First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk patients. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain, and relax anxiety of the patients and their relatives since RBCs transfusions probably have the strongest analgesic effects during the crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation all over the body. Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions will decrease transfusion-related complications including infections, iron overload, and blood group mismatch in the future. Fourthly, transfusion of RBCs suspensions in the secondary health centers may prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBCs, white blood cells (WBCs), platelets (PLTs), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis

by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For example, leukocytosis even in the absence of any infection was an independent predictor of the severity of the SCDs, and it was associated with the risk of stroke in a cohort of Jamaican patients (23). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (24), but according to our clinical experience, simple and repeated RBCs transfusions are highly effective both to relieve pain and to prevent sudden death that may develop secondary to multiorgan failures on the long-term inflammatory background of the SCDs.

Hydroxyurea may be the most effective life-saving drug for the treatment of the SCDs (25, 26). It interferes with the cell division by blocking the formation of deoxyribonucleotides by means of inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the suppression of leukocytosis and thrombocytosis by blocking the DNA synthesis in the SCDs (27, 28). By this way, the chronic inflammatory and destructive process of the SCDs is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As also seen in the viral hepatitis cases, although presence of a continuous damage of sickle cells on the capillary endothelium, the severity of destructive process is probably exaggerated by the patients' own WBCs and PLTs. So suppression of proliferation of them may limit the capillary endothelial damage, inflammation, edema, tissue ischemia, and end-organ failures all over the body (29). Similarly, final Hb F levels in hydroxyurea users did not differ from their pretreatment levels (30). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (31). The study especially researched effects of hydroxyurea on painful crises, ACS, and requirement of blood transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was initiated for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (31). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (31). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (31). Whereas we used all subtypes of the SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p < 0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p < 0.000$) (26). Parallel to our results, adult patients using hydroxyurea therapy for frequent painful crises appear to have reduced mor-

tality rate after a 9-year follow-up period (32). Although the underlying disease severity remains critical to determine prognosis, hydroxyurea may also decrease severity of the SCDs and prolong survival (32). The complications start to be seen even in infancy in the SCDs. For example, infants with lower hemoglobin values were more likely to have a higher incidence of clinical events such as ACS, acute painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (33). Hydroxyurea therapy in early years of life may improve growth, and prevent end-organ insufficiencies. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult. On the other hand, elevations of liver enzymes during some acute painful crises can not be reversed by withdrawing of the hydroxyurea therapy alone, instead withdrawal of all of the medications were highly effective in such cases during the 20-year experience on such patients. After normalization of the liver enzymes, the essential medications must be started one by one, instead of all of them at the same time again. Therefore hydroxyurea therapy must even be used during the acute painful crises in the SCDs. Additionally, we observed mild, moderate, or severe bone marrow suppressions and pancytopenia in some patients using high-dose hydroxyurea (35 mg/kg/day). Interestingly, such cases were completely silent other than some signs and symptoms of anemia, and all of them were resolved completely just by giving a few-day break for hydroxyurea therapy and starting with smaller doses again.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce pain, fever, inflammation, and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAIDs, it also suppresses the normal functions of PLTs, irreversibly. This property causes aspirin being different from other NSAIDs, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PGs) and thromboxanes (TXs) is due to its irreversible inactivation of the COX enzyme required for PGs and TXs synthesis. PGs are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation in the body. TXs are responsible for the aggregation of PLTs to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of TXA₂ in the PLTs, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLTs (8-9 days). Since PLTs do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin inhibited the enzyme. The antithrombotic property of aspirin is useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (34). Heart attacks are caused primarily by blood clots, and low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (35). According to the literature, aspirin may also

be effective in prevention of colorectal cancers (36). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease (37). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (38). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (38). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (38). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (37). Although the liver toxicity typically occurs in the syndrome, jaundice is usually not seen with it, but the liver is enlarged in most cases (37). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (38). Although the death occurs in 20-40% of affected cases, about one third of survivors get a significant degree of brain damage (37). About 90% of cases in children are associated with an aspirin use (39). Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 16 years (40). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (37). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% in rates of Reye syndrome was seen (38). Due to the higher side effects of corticosteroids in long term use, and due to the very low risk of Reye syndrome but much higher risk of death due to the SCDs even in children, aspirin should be added both into the acute and chronic phase treatments with an anti-inflammatory dose even in childhood in the SCDs (41).

ACS is a significant cause of mortality in the SCDs (42). It occurs most often as a single episode, and a past history is associated with a higher mortality rate (42). Similarly, all of 14 patients with ACS had just a single episode, and two of them were fatal in spite of the immediate RBCs and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the ten-year follow up period. ACS is the most common between two to four years of age, and its incidence decreases with aging (43). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, and the mean ages of the patients with ACS and SCDs were similar (30.3 vs 30.5 years, $p>0.05$, respectively). The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response by aging. Probably, ACS shows an inborn severity of the SCDs, and the incidence of ACS is higher in severe cases such as cases with the SCA and higher WBCs counts (42, 43). According to our experiences, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates with end-organ insufficiencies. ACS may also

be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the abnormal RBCs-induced diffuse capillary endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBCs and PLTs (44). Similarly, we strongly recommend hydroxyurea therapy for all patients with the SCDs that may also be the cause of the low incidence of ACS among our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% of cases (42, 43), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (45). Beside that some authors indicated that antibiotics do not shorten the clinical course (46). RBCs support must be given early in the course of ACS. RBCs support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBCs and excessive WBCs and PLTs. So they prevent further sickling, capillary endothelial damage, exaggerated capillary endothelial inflammation and edema, tissue hypoxia, and end-organ insufficiencies all over the body.

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (47). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization, there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (48). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (49). Onset is typically seen between 20 and 60 years of age (48). The most common causes are CHD and COPD (48, 50). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (51). But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (51). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (51). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (51). On the other hand, PHT is also a common consequence of the SCDs (52), and its prevalence was detected between 20% and 40% in the SCDs (53). Whereas we detected

the ratio as 12.2% in the present study. Although the higher prevalences of smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic risk factors or consequences in male gender, and the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic natures of PHT and ACS in SCDs in the present study. Additionally, frequencies of DVT and/or varices and/or telangiectasias were similar in males and females parallel to ACS and PHT (9.0% vs 6.6%, $p > 0.05$, respectively). Similarly, CHD is the other most common cause of PHT in the society (54), and although the higher prevalence of CHD in males in the present study (18.0% vs 13.2%, $p < 0.05$), PHT was not higher in males, again. In another definition, PHT may have a hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCDs (55, 56), since the mean age of ACS is lower than PHT (30.3 and 34.0 years, $p < 0.05$), and its mortality is much higher than PHT (42, 43, 48).

COPD is the third leading cause of death with various underlying etiologies in whole world (57, 58). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess weight, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Beside smoking, regular alcohol consumption is also important for the pulmonary and systemic inflammatory process of the COPD, since COPD was one of the most common diagnoses in alcohol dependence (59). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (60). Probably an accelerated atherosclerotic process is the main structural background of functional changes that are characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (61, 62). For example, there may be close relationships between COPD, CHD, PAD, and stroke (63). Furthermore, two-third of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (64). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (64). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (65). On the other hand, COPD may be the pulmonary consequence of the systemic atherosclerotic process caused by the hardened RBCs in the SCDs (57).

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (66).

Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (67). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, and hepatic diseases and smoking which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect their functions in a short period of time. On the other hand, digital clubbing is also common in the SCDs, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p < 0.001$) may also show some additional role of male gender in the systemic atherosclerotic process.

Leg ulcers are seen in 10% to 20% of the SCDs, and the ratio was 13.5% in the present study (68). Its prevalence increases with aging, male gender, and SCA (69). Similarly, its ratio was higher in males (19.8% vs 7.0%, $p < 0.001$), and mean age of the leg ulcer cases was higher than the remaining patients (35.3 vs 29.8 years, $p < 0.000$) in the present study. The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (68). As an evidence of their atherosclerotic nature, the leg ulcers occur in the distal segments of the body with a lesser collateral blood flow (68). The hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major causes, again (69). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The hardened RBCs-induced venous insufficiencies may also accelerate the process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs (70). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (71). Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBCs counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage (30). According to our experiences, prolonged resolution of leg ulcers with hydroxyurea

may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema instead of the fibrosis, yet.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (72). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (72). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (73). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (74). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs (75). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (76). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (77). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (77, 78). As a result, cirrhosis may also be another atherosclerotic consequence of the SCDs.

The increased frequency of CRD can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (79, 80). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, inflammatory or infectious processes, and cancers may be the main underlying causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts. Excess weight-induced hyperglycemia, dyslipidemia, elevated BPs, and insulin resistance may cause tissue inflammation and immune cell activation (81). For example, age ($p=$

0.04), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BPs ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (80). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BPs with excess weight (82). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (82). However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (83). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much more easily (82). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (84). Although some authors reported that alcohol was not related with the CRD (84), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (77). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (85). For example, the most common cause of death was the cardiovascular diseases in the CRD again (86). The hardened RBCs-induced capillary endothelial damage in the renal vasculature may be the chief cause of CRD in the SCDs. In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCDs, again (87).

Stroke is an important cause of death, and usually develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is a common complication of the SCDs, too (88, 89). Similar to the leg ulcers, stroke is especially higher with the SCA patients and cases with higher WBCs counts (90). Sickling-induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may cause chronic capillary endothelial inflammation, edema, and fibrosis (91). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs counts-induced exaggerated capillary inflammation, edema, and

fibrosis (91). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial inflammation, edema, and fibrosis may be much more important. Infections, inflammations, medical or surgical emergencies, and emotional stresses may precipitate stroke by increasing basal metabolic rate and sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs counts-induced exaggerated capillary inflammation, edema, and fibrosis (44).

The venous endothelium is also involved in the SCDs (92). Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in the upright position. Although the relatively younger mean ages of the cases and significantly lower mean body mass index of the SCDs cases in the medical literature (10), the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the present study (9.0% vs 6.6% in males and females, $p>0.05$, respectively), indicating an additional venous involvement of the SCDs. Similarly, priapism is the painful erection of penis that can not return to its flaccid state within four hours in the absence of any stimulation (93). It is an emergency since repeated damaging of the blood vessels may terminate with fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (93). It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (94, 95). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types (96). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood can not return adequately from the penis as in the SCDs, and they are very painful (93, 96). The other 5% are nonischemic (arterial) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system (93). Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia (93). RBCs support is the treatment of choice in acute phase whereas hydroxyurea should be the treatment of choice in chronic phase (97). According to our experiences, hydroxyurea is effective for prevention of attacks and consequences of priapism if initiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

As a conclusion, the hardened RBCs-induced capillary endothelial damage, inflammation, edema, and fibrosis are initiated at birth, and terminate with disseminated tissue hypoxia and multiorgan failures even at childhood in the SCDs. Although RBCs supports and corticosteroids in acute phase and aspirin plus hydroxyurea both in acute

and chronic phases decrease severity of the diseases, survivals are still shortened in both genders, dramatically. Infections, medical or surgical emergencies, or emotional stresses-induced increased basal metabolic rate aggravates the sickling and capillary endothelial edema, and may terminate with acute painful crises, multiorgan failures, and sudden deaths.

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Role of glucagon-like peptide-1 analogues in weight management

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Bilal Hasan Chaudhry, Laith AlMarsomi. Role of glucagon-like peptide-1 analogues in weight management. World Family Medicine. June 2023; 21(5): 50- 51 DOI: 10.5742/MEWFM.2023.95256110

Abstract

Obesity is a growing concern in all parts of the world. It carries major health concerns which are in turn translated into financial costs. Alongside patient education and guidance, both surgical and pharmacological methods are being employed to control weight. A major breakthrough in this regard has been introduction of glucagon-like peptide-1 analogues (GLP-1), which have now been approved for use in weight management(1).

Key words: weight management, glucagon-like peptide-1 analogues,

Introduction

The economic impact of overweight and obesity in 2019 is estimated at 2.19% of global gross domestic product (GDP). If current trends continue, by 2060, the economic impacts from overweight and obesity are projected to rise to 3.29% of GDP globally(2). There are a number of reasons why people can gain weight. Logically foremost is overeating and sedentary lifestyle(3). Genetics can play a role as in how the body stores and processes fat, making some people more prone to weight gain than others(4). Hormonal imbalances, such as hypothyroidism or insulin resistance, can also contribute to weight gain(5). Other medical conditions such as polycystic ovary syndrome (PCOS), Cushing's syndrome, and Prader-Willi syndrome also play a role in weight gain. Alongside these, certain medications, such as antidepressants, antipsychotics, and steroids, can be the contributing factor in weight gain for some.

An ageing population means slow metabolism, which can lead to weight gain if they do not adjust their calorie intake or physical activity level(6). Another important factor is stress. Chronic stress can cause hormonal changes that contribute to weight gain. Foss et al raised the question whether stress in obesity is cause or consequence?(7). A lack of sleep which is closely related to stress can affect hormones that regulate appetite, leading to increased cravings and overeating(8).

It is important to address the underlying factors that contribute to weight gain to create a sustainable weight loss plan. This may involve changes in diet, physical activity level, stress management, medication adjustments, or treatment for any underlying medical conditions and now the introduction of new medication.

Discussion

GLP-1 (glucagon-like peptide-1) analogues are a class of medications used in the treatment of type 2 diabetes and obesity. GLP-1 is a hormone that is naturally produced in the gut and helps regulate blood sugar levels by stimulating insulin release and suppressing glucagon secretion. GLP-1 analogues mimic the effects of natural GLP-1 and are used to lower blood sugar levels in people with diabetes.

In addition to their effects on blood sugar levels, GLP-1 analogues have also been found to promote weight loss. GLP-1 analogues work by reducing appetite and increasing feelings of fullness (satiety), which can lead to a reduction in calorie intake and subsequent weight loss.

Several GLP-1 analogues are currently approved for the treatment of obesity, including liraglutide (Saxenda) and semaglutide (Wegovy)(9). These medications are typically used in conjunction with lifestyle changes, such as a healthy diet and exercise, to achieve and maintain weight loss.

Studies have shown that treatment with GLP-1 analogues can lead to significant weight loss, with some people losing up to 10% of their body weight over the course of several months(10). Rubino et al showed a weight loss of 18% overall and continued weight loss after 20 weeks with continuation of Semaglutide as opposed to switching to placebo(11). Wilding et al report a weight loss of 15% or more for 50.5% of the patients studied (12). Additionally, GLP-1 analogues have been found to improve other health outcomes in people with obesity, such as reducing blood pressure and improving lipid profiles (13).

However, it is important to note that GLP-1 analogues are not appropriate for everyone and can have side effects, such as nausea, vomiting, and diarrhea. While most patients will find these to be mild and transient some may not be able to continue with medication. Wilding et al found that 4.5% of the patients discontinued Semaglutide due to gastrointestinal side effects(12). These medications should only be used under the guidance of a healthcare provider and as part of a comprehensive weight management plan.

Surgical vs pharmacological weight management

Bariatric surgery and GLP-1 analogues are both options for weight management, but they have different mechanisms of action and potential risks and benefits. Bariatric surgery typically leads to greater weight loss than GLP-1 analogues, with an average weight loss of 30-40% of excess body weight compared to 15-20% for GLP-1 analogues(14).

Bariatric surgery is a major surgical procedure that carries risks such as bleeding, infection, and complications related to anesthesia. GLP-1 analogues are generally well tolerated but can have side effects such as nausea, vomiting, and diarrhea.

Bariatric surgery also carries a huge financial cost which is more than GLP-1 analogues and in some cases that cost may not be covered by insurance.

Both bariatric surgery and GLP-1 analogues can lead to improvements in obesity-related health conditions such as type 2 diabetes, high blood pressure, and sleep apnoea.

Conclusion

While GLP-1 analogues play a huge role in weight management it is important to address the underlying factors that contribute to weight gain to create a sustainable weight loss plan. This may involve changes in diet, physical activity level, stress management, medication adjustments, or treatment for any underlying medical conditions.

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Helicobacter Pylori infection; the challenging task of improving eradication rates in light of rising antibiotic resistance, a literature review

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Asad Islam. Helicobacter Pylori infection; the challenging task of improving eradication rates in light of rising antibiotic resistance, a literature review. World Family Medicine. June 2023; 21(5): 52-59

DOI: 10.5742/MEWFM.2023.95256112

Abstract

Helicobacter pylori (*H. pylori*) infection continues to be a major public health issue worldwide. A global systematic review shows that in 2015, approximately 4.4 billion individuals worldwide were estimated to be positive for *H. pylori*. Overwhelming evidence has demonstrated that *H. pylori* infection is associated with significant medical conditions including peptic ulcer disease, stomach cancer and MALToma. The consensus report from the Kyoto *H. pylori* conference in 2015 recommended that all *H. pylori* infections should be eradicated whenever they are found unless there are compelling reasons not to do so. However, increasing *H. pylori* antibiotic resistance has been reported globally over the past two decades coinciding with a continuous decrease in eradication success rates. To tackle this global problem, we need new antimicrobial drugs and treatment strategies but also a better understanding of the emergence and spread of resistant bacteria as well as improved diagnostic tools to guide clinicians in further optimizing currently available regimens.

Key words: Helicobacter pylori, eradication, antibiotic resistance,

Introduction and Epidemiology

Helicobacter pylori (*H. pylori*) infection continues to be a major public health issue worldwide. A global systematic review shows that in 2015, approximately 4.4 billion individuals worldwide were estimated to be positive for *H. pylori* (1). Infection is more frequent and acquired at an earlier age in resource-limited countries compared with industrialized nations(2). Other studies have also found that the risk of acquiring *H. pylori* infection is related to socioeconomic status and living conditions early in life. Factors such as density of housing, overcrowding, number of siblings, sharing a bed, and lack of running water have all been linked to a higher acquisition rate of *H. pylori* infection(3–6).

The problem of recurrence of *H. pylori* infection after successful treatment also appears closely associated with socioeconomic and sanitary conditions. In a systematic review and meta-analysis of 132 studies that included 53,934 patient-years, globally; the recurrence rate was inversely related to the human development index and directly related to *H. pylori* prevalence (7).

Microbiology

H. pylori is a spiral shaped, micro-aerophilic, multi-flagellate gram-negative bacterium measuring approximately 3.5 microns in length and 0.5 microns in width(8). It can be biochemically characterized as catalase, oxidase, and urease positive. Urease, produced in abundance making up more than 5 percent of the organism's total protein weight, appears to be vital for its survival and colonization. It is also clinically important because it forms the basis for several invasive and noninvasive tests to diagnose infection. The organism's urease activity, motility, and ability to adhere to gastric epithelium are factors that allow it to survive and

proliferate in the gastric milieu (9). Disruption of urease activity, bacterial mobility, or attachment prevents *H. pylori* colonization (10). Bacterial urease hydrolyzes gastric luminal urea to form ammonia that helps neutralize gastric acid and form a protective cloud around the organism, enabling it to penetrate the gastric mucus layer (11).

Disease Association

Although overwhelming evidence has demonstrated that *H. pylori* infection is bad for humans, in the past some have questioned the wisdom of eradicating the infection in all those infected. Their arguments are largely based on hypothesis and circumstantial evidence:

- 1) Less than 20% of all *H. pylori* infected persons will develop significant clinical consequences in their lifetime.
- 2) *H. pylori* strains are highly diverse at a genetic level and are of different virulence.
- 3) The antiquity of *H. pylori* infection in humans and their co-evolution suggests that *H. pylori* may be a commensal to humans. Eradication of *H. pylori* may remove some beneficial bacterial strains and may provoke oesophageal disease or gastric cancer at the cardia. However, careful review of the literature confirms that *H. pylori* infection is a serious pathogen albeit in a minority of those infected. It remains for carefully designed prospective studies, rather than hypothesis, to make changes in the current consensus position(3).

Below is an overview of some of the evidence linking *H. pylori* to clinically significant medical conditions.

Peptic Ulcer disease

Various aspects of *H. pylori* infection suggest strong association with Peptic Ulcer disease; firstly, *H. pylorus* is present in most patients who have a duodenal ulcer that is not related to NSAID use. Early studies noted a high incidence of *H. pylori* infection in patients with duodenal ulcers(12). Subsequent reviews confirmed that *H. pylori* is detectable in 80 to 95 percent of these patients(13,14). These data were supported by reports which found that the prevalence of *H. pylori* is negligible in populations in which ulcer disease is rare (15).

Secondly, *H. pylori* infection is detectable before the occurrence of duodenal ulcers and appears to be a risk factor for the disorder. Several trials have found that pre-existing *H. pylori* infection is a risk factor for the development of duodenal ulcers(16–18).

Thirdly, treatment of *H. pylori* infection in patients with duodenal ulcers decreases the incidence of ulcer recurrence. One meta-analysis examined the recurrence rate for duodenal ulcer after at least six months of follow-up. The recurrence rate was 6 percent if *H. pylori* was eradicated and 67 percent if it was not(19). A second meta-analysis found recurrence rates of 20 and 56 percent, respectively(20).

The studies in the meta-analyses used endoscopic findings to define ulcer recurrence. It should be noted that the rate of symptomatic recurrence is lower.

Gastric cancer

The International Agency for Research on Cancer estimates that 36 and 47 percent of all gastric cancers in developed and developing countries, respectively, are solely attributable to *H. pylori* infection. This accounts for almost 350,000 gastric cancers annually worldwide. One report indicated that of the 12.7 million new cancers occurring in 2008, the population attributable fraction due to infections was over 16 percent for *H. pylori*(21).

Two meta-analyses of cohort and case control studies examining the relationship between *H. pylori* sero-positivity and gastric cancer found that *H. pylori* infection was associated with a twofold increased risk for developing gastric adenocarcinoma(22,23).

One of the largest prospective studies addressing *H. pylori* and cancer risk included 1,526 Japanese patients of whom 1,246 had *H. pylori* infection(24). Patients underwent endoscopy with biopsy at enrollment and then again between one and three years after enrollment. During a mean follow-up of 7.8 years, 36 patients developed gastric cancer (2.9 percent), all of whom were *H. pylori* infected. No uninfected patient developed cancer(24).

MALToma

Multiple studies have demonstrated an association between *H. pylori* infection and MALToma, (mucosa (gut)-associated lymphoid tissue tumor) and have begun to elucidate the mechanisms underlying this association(25–31).

The most dramatic evidence supporting a pathogenetic role for *H. pylori* in MALToma is remission of the tumor following eradication of *H. pylori* with antibiotic therapy(32–39).

Rationale for *H. Pylori* eradication

In the absence of an effective vaccine, treatment of chronic *H. pylori* infection has emerged as the main strategy for reducing the spread of bacteria in the population, for resolving gastric lesions in infected patients, and for preventing subsequent gastric cancer development(40). Furthermore, the consensus report from the Kyoto *H. pylori* conference in 2015 signaled a fundamental shift in thinking and recommended that all *H. pylori* infections should be eradicated whenever they are found unless there are compelling reasons not to, such as co-morbidities, high re-infection rates in the country and competing health priorities of society(41,42).

Treatment strategies

The American College of Gastroenterology guidelines for *H. Pylori* infection recommend that the choice of initial antibiotic regimen to treat *H. pylori* should be guided by the presence of risk factors for macrolide resistance and the presence of a penicillin allergy(43). A resistance threshold of ≥ 15 percent in the community is commonly used for choosing alternative empiric antibiotic regimen for *H. pylori*(44,45).

Clarithromycin triple therapy consisting of a PPI, Clarithromycin, and Amoxicillin or Metronidazole for 14 days remains a recommended treatment option in regions where *H. pylori* Clarithromycin resistance is known to be <15% and in patients with no previous history of macrolide exposure for any reason(43). In regions where the rate of Clarithromycin resistance is known to be high or if a patient has previously been treated with macrolides for any reason, Bismuth quadruple therapy should be strongly considered as the initial treatment choice(43).

Unlike Clarithromycin triple therapy, the efficacy of Bismuth quadruple therapy is not affected by Clarithromycin resistance. Also, although Metronidazole resistance does have an impact on the efficacy of Bismuth quadruple therapy, it is not nearly as profound as that of Clarithromycin resistance on Clarithromycin triple therapy(46).

Other regimes have been trialled and suggested like hybrid, sequential and concomitant(47–49).

However, the complexity of the treatment regimen has limited its use as a first-line regimen in the treatment of *H. pylori*.

Role of probiotics

There is growing interest in the United States of probiotics as adjuvant therapy in the treatment of *H. pylori* infection. Emerging evidence suggests an inhibitory effect of *Lactobacillus* and *Bifidobacterium* species on *H. pylori*(43). The addition of probiotics to *H. pylori* therapies has been acknowledged as improving eradication rates whilst reducing the adverse effects of regimens and counteracting the harmful effects of antimicrobials on the gut microbiota. In different meta-analyses, compared to events noted with control therapies, probiotics globally improved *H. pylori* eradication rates by >10% while preventing >50% of total drug-related adverse effects and antibiotic-associated diarrhoea(50–52).

A recent meta-analysis of 10 clinical trials of adjuvant probiotics in patients with *H. pylori* infection demonstrated increased cure rates with probiotic supplementation (pooled OR, 2.07; 95% CI, 1.40–3.06) (53). Probiotics also reduced the incidence of total side effects (pooled OR, 0.31; 95% CI, 0.12–0.79).

The issue of antibiotic resistance

Increasing *H. pylori* antibiotic resistance has been reported globally over the past two decades coinciding with a continuous decrease in eradication success rates(54–57).

In a systematic review and meta-analysis that included 178 studies, comprising 66,142 isolates from 65 countries, primary and secondary resistance to Clarithromycin, Metronidazole, and Levofloxacin were high (≥ 15 percent) in the majority of WHO (World Health Organization) regions. Resistance to Clarithromycin was significantly associated with failure of *H. pylori* eradication with a Clarithromycin-containing regimen (odds ratio, 6.97; 95% CI, 5.2–9.3) (57).

Local surveillance data are needed to guide the choice of eradication regimens.

Many studies have shown this rising resistance to have direct impact on the efficacy of the most commonly used eradication regimes. In a meta-analysis, data from 93 studies with 10,178 participants was analysed. For triple therapies, Clarithromycin resistance had a greater effect on treatment efficacy than Nitroimidazole resistance. Drug resistance was a strong predictor of efficacy across triple therapies for the eradication of *H. pylori* in adults(58).

Multiple factors have been reported to play a role in this rapid development of primary antibiotic resistance in *H. pylori*. These include limited choice of effective therapeutics; the extensive use of certain antibiotics in the general population (such as Clarithromycin for respiratory infections); the exceptional adaptation ability of the species(55,59). Thus, since 2017, *H. pylori* has been listed by the WHO among the 20 pathogens that pose the most serious threat to human health because of their drug resistance(60).

The worrying issue of Multi-drug resistance

The alarming presence of *H. pylori* strains with a MDR (Multi-drug resistant) profile, such as simultaneous resistance to three or more drug families, is increasingly noted within the global emergence of antibiotic resistance in the species(61).

Clinical implications of drug resistance

The main clinical implication of bacterial resistance in vitro is a substantial decrease in *H. pylori* treatment efficacy with, theoretically, a subsequent increase in clinical complications such as gastric cancer or peptic ulcers following increased persistence of infections(57). Pretreatment antibiotic resistance has been identified as the most important factor in non-response to *H. pylori* treatment(62,63).

To tackle this global problem, we need new antimicrobial drugs and treatment strategies but also a better understanding of the emergence and spread of resistant bacteria as well as improved diagnostic tools to guide clinicians in further optimizing currently available regimens(64).

Molecular mechanisms of drug resistance

Understanding the mechanistic and biological attributes that drive antibiotic resistance in *H. pylori* species has increased greatly over the past two decades, mainly for resistance against specific families of antimicrobials that are commonly used in *H. pylori* eradication therapies (that is, β -lactams, fluoroquinolones, macrolides, nitroimidazoles, tetracyclines and rifamycins) (64). For example in the case of Amoxicillin, *H. pylori* species, despite encoding several putative PBPs (Penicillin-binding proteins) and β -lactamase-like proteins, develop Amoxicillin resistance mainly by reducing the binding affinity to a specific PBP named PBP1A without generating substantial β -lactamase activity(65–67). Among macrolides, Clarithromycin has been used in front-line regimens for *H. pylori* eradication

given its two pharmacokinetic advantages in the stomach: acid stability and improved absorption in the gastric mucus layer(68,69). In *H. pylori*, the main mechanism underlying Clarithromycin resistance is point mutations in domain V of the 23S rRNA gene, namely A2142G/C and A2143G mutations(70–72).

Detection of antibiotic resistance

With the growing prevalence of global antibiotic resistance in *H. pylori* infection, antibiotic susceptibility testing (AST) is becoming increasingly needed for guiding decisions about appropriate therapies in individuals and treatment policies in populations(41,54,73). Several testing techniques have been developed in *H. pylori* for dealing with various challenges in terms of timing, costs and different required analytical specimens. These techniques can be categorized into culture-based and molecular-based AST techniques(64).

Culture-based AST techniques

Culture-based techniques are the standard AST for *H. pylori* using either the agar dilution method or the Epsilometer test (E-test) method(54). Culture-based techniques provide in vitro phenotypic susceptibility information. These techniques are useful quantitative methods for determining the minimum concentration of an antimicrobial agent that kills (bactericidal activity) or inhibits the growth (bacteriostatic activity) of *H. pylori* after around 72 hours of incubation. The agar dilution method can be adapted for testing several strains at once on the same medium plate, enabling a high-throughput AST. The E-test method is less technically challenging and less time-consuming(64).

However, both methods have important limitations in *H. pylori*. First, they raise challenges owing to the pathogen's fastidious growth requirements, restricting the phenotypic AST assay to only well-equipped laboratories with well-trained technicians. Second, interpretation of phenotypic outcomes is strongly dependent on the experimental conditions and hence can be subjective whilst not being always reproducible(74). For instance, Metronidazole susceptibility testing can potentially be affected by redox variations in the test medium(62). Finally, assessing the phenotypic resistance in *H. pylori* is time consuming and delivers results, after strain isolation, in about one week in the best case(75,76). It is therefore particularly challenging to implement these procedures in clinical practice, especially in regions with high *H. pylori* prevalence, as all these factors prevent regions with limited resources from performing routine phenotypic AST of *H. pylori*, and more rapid and cost-effective molecular methods that enable reliable prediction of phenotypic drug resistance are needed(65,77).

Molecular-based AST techniques

Advances in the understanding of basic molecular aspects of drug resistance in *H. pylori* have enabled the development of several methods for rapid detection of resistance during clinical infections. These methods rely

mainly on the detection of specific *H. pylori* mutations encoding resistance, but differ in their respective turn-around times, types of analytical specimen and performance(64).

Importantly, these assays can either be culture-based when performed on cultured isolates or culture-free when directly applied on various types of biological specimens such as fresh, frozen or paraffin-embedded gastric biopsy samples, stool samples and gastric juice(78–88). These assays can be highly reliable but their accuracy might be affected by the condition of the samples, and by possible DNA contamination or degradation(86).

For instance, stool samples in which there might be a low amount of *H. pylori* DNA require powerful DNA extraction techniques to achieve good results. Paraffin embedding of gastric biopsy samples can lead to false-negative results because the fixative can break DNA into small pieces(87–89).

Meanwhile, the clinical relevance of molecular assays can be affected by their high sensitivity that can detect dead or non-cultivable microorganisms(86).

Moreover, DNA sequencing by the Sanger method, the gold standard for identifying mutations following PCR, is not cost-effective in a routine setting(87).

Numerous PCR-based methods are available for detecting only a few specific mutations and offer cost-efficient advantages, namely for resistance to Clarithromycin, Tetracycline and Levofloxacin. In particular, several molecular-based kits that detect both the presence of *H. pylori* and the mutations associated with Clarithromycin resistance are commercially available, and can provide a result in a few hours and can be performed by any microbiology laboratory(87).

By contrast, establishing assays for detecting resistance to Metronidazole and Amoxicillin has remained difficult probably due to the wide diversity of underlying molecular mechanisms.

NGS (Next-generation sequencing) Technology:

NGS technologies have emerged as a powerful and fast tool for antibiotic resistance prediction and surveillance(65, 90–95). To predict antibiotic resistance in *H. pylori*, NGS approaches would be applied in combination with bacterial culture for bacterial whole-genome sequencing (WGS) or with other molecular techniques (such as PCR) for deep-amplicon sequencing. NGS-based methods present several advantages over traditional molecular methods. Antibiotic resistance in clinical *H. pylori* isolates often arises from scattered sequence positions (such as mutations in genes e.g. *pbp1A* and *rdxA*), requiring the molecular-based approach to cover a sufficient sequence length to reach its highest performance. Classic PCR-based methods (PCR with Sanger sequencing) face limitations as they can accurately target only a limited number of nucleotides and cannot theoretically cover all possible complex structural variants of resistance-related

genotypes encountered in *H. pylori* (for example, large deletions or insertions in *rdxA* gene). These methods are hence prone to false-negative results.

By contrast, NGS-based approaches provide a more comprehensive view of bacterial genotypes and are particularly relevant for tracking complex or nested genetic factors driving antibiotic resistance with interesting potential for the discovery of novel or rare resistance mechanisms in clinical isolates(65,91,92,94–96).

In addition, NGS can be performed within a clinically relevant timeframe (24–72 hours) (65,75,90).

Unlike deep amplicon sequencing, whole-genome sequencing (WGS) methods require an initial cultivation of *H. pylori*, but this limitation is ready to be overcome with new advances in metagenome-assembled genomics(65,75,97,98).

Currently, several NGS technologies can probably be afforded even by laboratories located in low-income regions. Exploiting bacterial genomics via WGS is therefore a highly attractive option for tracking *H. pylori* antibiotic resistance in diagnostic microbiology laboratories compared with phenotypic AST and antibiotic resistance genotyping by classic PCR-based molecular methods(75).

However, in general, given the analytical challenges raised by high-throughput NGS data, further work is currently needed for standardization and implementation of easy-to-use computational tools for detecting resistance-related genetic determinants(65,91,92,94,95).

Conclusion

Based on the lack of a readily available vaccine in the very near future, other directions for counteracting *H. pylori*-related drug resistance have to be considered. The first option is to optimize the effectiveness of available empirical regimens for *H. pylori* eradication(64).

While we wait for an effective vaccine and further development of the novel susceptibility testing techniques for specific drugs, we should use the most likely effective first line combination therapy. This may vary according to local resistance data and antibiotic use and local guidelines should be developed for this. This will minimise delay in treatment while at the same time avoiding recurrent failure to rescue therapies, ultimately leading to the overuse of antibiotics, worsening resistance. If this fails to achieve eradication, then local strategies should be available for the patient to undergo endoscopy and sensitivities before using further empirical therapies.

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Use of Uterine and Ovarian Arteries Doppler Parameters for the Prediction of Infertility in Females

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Syed Muhammad Yousaf Farooq et al. Use of Uterine and Ovarian Arteries Doppler Parameters for the Prediction of Infertility in Females. World Family Medicine. June 2023; 21(5): 60-65

DOI: 10.5742/MEWFM.2023.95256113

Abstract

Background: In the context of fertility, Doppler sonography is used to evaluate the blood flow to the uterus and ovaries. The blood flow to these organs plays a crucial role in the process of ovulation, fertilization, and implantation of the fertilized egg. Changes in the Doppler sonographic indices of the uterine and ovarian arteries can provide information about the blood flow to these organs and can help identify potential problems that may be affecting fertility.

Objective: To evaluate the Doppler indices of uterine and ovarian arteries in fertile and infertile women and help clinicians develop more effective diagnostic and treatment strategies for infertility.

Methodology: A cross-sectional Analytical study was conducted for a duration of 9 months at a Medics Dr. Amers, Lahore, Pakistan. The study included 150 fertile and 150 infertile females aged 18-45 and excluded all females using oral contraceptive and contraceptive devices. SPSS software version 25 was used to analyze the data.

Results: Age of participants ranged between 19 to 43 years with a mean + SD age of 28 + 6.5 years. The mean + SD RI and PI of left ovarian artery was 0.48 + 0.03 and 1.1 + 0.13 in the fertile, 0.9 + 0.03 and 4.2 + 1.2 in the infertile group. The mean + SD RI and PI of right ovarian artery was 0.60 + 0.03 and 1.6 + 0.06 in the fertile, 0.8 + 0.01 and 3.0 + 0.4 in the

infertile group (Table 1) Overall, results shows that the four variables are significantly different between fertile and infertile groups, with higher values in the infertile group.

Independent sample test showed statistical significance between RI and PI of right ovarian artery of both groups ($P < 0.05$). However, in left ovarian artery the values of PI in both groups showed a significance ($P < 0.05$) were as values RI are found to be insignificant ($P > 0.05$). Independent sample test showed statistical significance between RI and PI of right and left uterine artery of both groups ($P < 0.05$). The mean + SD endometrial thickness in fertile group was 11.0 + 2.6 mm it was 9 + 1.6 mm in infertile group (Table 3). Indicating a significant difference between the two groups ($P < 0.05$).

Conclusion: Uterine and Ovarian artery hemodynamics plays an important role in fertility. Findings from this study revealed that a high RI and PI and thin endometrium significantly affects fertility.

Key words: Resistive index, Pulsatility index, Infertility, Uterine artery, Ovarian artery.

Introduction

The ability to have children is known as fertility, and a couple is deemed infertile if they are unable to conceive after 12 months of unprotected sexual activity. A stricter definition of infertility includes failure to conceive within six months for individuals over 35 and failure to become pregnant within a year for people under 35 (1). According to estimates, one in seven to one in five (14–20%) couples of reproductive age have infertility globally. Ovulatory problems, tubal illness, endometriosis, chromosomal abnormalities, sperm factors, and unexplained infertility are some of the causes of infertility that can affect men, women, or a combination of both sexes. The majority of infertility cases, including those caused by male and female causes, are treated surgically and medically. Age-related infertility continues to be one of the hardest problems despite the fact that infertility therapy has evolved significantly in recent years. When a couple is considering assisted reproductive technologies, age must be taken into consideration. Since many years ago, people have been aware that a woman's age and the likelihood of pregnancy are inversely associated (2).

Infertility rates differ between communities mostly because of differences in food habits, way of life, environmental and work-related factors, and infectious diseases. Unfortunately, infertility affects both male and female partners, and a broad list of diagnostic procedures are needed to make a diagnosis. Do an infertility evaluation as the first step in overcoming infertility? A physical examination, which includes a pelvic ultrasound of the female patient, a semen study, and the medical and sexual histories of both spouses are all included in the evaluation of infertility. A thorough physical examination, as well as a full medical, sexual, and reproductive history, are used to evaluate infertile women (3).

There are two types of infertility, primary and secondary (4). While secondary infertility is defined as the inability to conceive after a prior pregnancy, primary infertility is defined as the failure to conceive within two years of unprotected intercourse (5). Secondary infertility is associated with reproductive tract infections (6). The causes of female infertility are difficult to diagnose sometimes (7). A serious health problem that affects people all around the world is infertility (8). 186 million people experience infertility globally (9-11). The medical condition of infertility may have an impact on a patient's emotional, physical, mental, spiritual, and medical well-being (12).

Almost one-third of women struggle with infertility. Age raises the chance of infertility. According to estimates, 8 to 12 percent of couples worldwide are affected (13). Nonetheless, males account for 20–30% of cases of infertility (14). Infertility is prevalent in Pakistan at 22%, with primary infertility accounting for 18% of cases and secondary infertility for 4% of cases (15). Studies have found that the death risk in infertile women has increased to 10% (16). Radiographic imaging is crucial in evaluating female infertility because it might be challenging to diagnose

at times (17). Hysterosalpingography, hystero-graphy, pelvic ultrasound (US), and magnetic resonance imaging (MRI) are common imaging modalities (18).

The study's objective was to examine the measurements of uterine artery Doppler indices, such as the resistance index (RI), pulsatility index (PI), and systolic/diastolic (S/D) ratio, in fertile and infertile females and to look into their relationship with infertility. Congenital abnormalities, abnormal semen analysis, unexplained infertility, endometriosis, or multifactorial artery impedance were the causes of infertility in these women, and it was not able to forecast obstetric difficulties or evaluate uterine artery impedance in these individuals. The lack of information about the local population led to the current study's execution.

Materials and Methods

A cross-sectional Analytical study was conducted for a duration of 9 months at Medics DrAmers, located in Lahore. Study included 150 fertile and 150 infertile females aged 18-45. Fertile group included all multiparous females and excluded all females on oral contraceptives and IUCDs. Study group included nulliparous females with no known gynecological disease. All participants underwent trans abdominal ultrasound with full bladder using 3-5 MHz curvilinear probe. Patient lay in supine and ultrasound gel was placed on the transducer and the skin to allow for smooth movement of the transducer over the skin and to eliminate air between the skin and the transducer for the best sound conduction. AIUM guidelines were followed to scan patient. Color doppler was used to assess RI, PI values of ovarian and uterine arteries. Data was evaluated and analyzed with Statistical Software for Social Sciences (SPSS version 25.0). Independent sample t-test was applied to check the association between doppler parameters and infertility Value of P <0.05 was taken as significant.

Results

The mean + SD age of participants was 28 + 6.5 years. The mean + SD endometrial thickness in all 300 participants was 10.0 + 2.4 mm. The mean + SD RI and PI of left ovarian artery was 0.48 + 0.03 and 1.1 + 0.13 in fertile, 0.9 + 0.03 and 4.2 + 1.2 in infertile group. The mean + SD RI and PI of right ovarian artery was 0.60 + 0.03 and 1.6 + 0.06 in fertile, 0.8 + 0.01 and 3.0 + 0.4 in infertile group (Table 1) Overall, results shows that the four variables are significantly different between fertile and infertile groups, with higher values in the infertile group.\

Independent sample test showed statistical significance between RI and PI of right ovarian artery of both groups ($P < 0.05$). However, in left ovarian artery the values of PI in both groups showed a significance ($P < 0.05$) were as values RI are found to be insignificant ($P > 0.05$).

The mean + SD RI and PI of left uterine artery was 0.50 + 0.02 and 0.8 + 0.06 in fertile, 0.9 + 0.03 and 2.7 + 0.16 in infertile group. The mean + SD RI and PI of right uterine artery was 0.65 + 0.04 and 1.5 + 0.17 in fertile, 0.83 + 0.01 and 2.3 + 0.11 in infertile group (Table 2). Independent sample test showed statistical significance between RI and PI of right and left uterine artery of both groups ($P < 0.05$).

The mean + SD endometrial thickness in fertile group was 11.0 + 2.6 mm it was 9 + 1.6 mm in infertile group (Table 3). Indicating a significant difference between the two groups ($P < 0.05$).

The mean + RI an PI of Left ovarian artery in age group 19-30 was 0.6 + 0.2 and 2.6 + 1.7, in age group 31-43 years 0.7 + 0.2 and 2.8 + 1.7. The mean + RI an PI of Right ovarian artery in age group 19-30 was 0.70 + 0.1 and 2.2 + 0.75, in age group 31-43 years 0.72 + 0.1 and 2.4 + 0.7. The mean + RI an PI of Left uterine artery in age group 19-30 was 0.69 + 0.2 and 1.7 + 0.9, in age group 31-43 years 0.73 + 0.2 and 1.9 + 0.9. The mean + RI an PI of Right uterine artery in age group 19-30 was 0.73 + 0.09 and 1.9 + 0.42, in age group 31-43 years 0.75 + 0.0.9 and 2.0 + 0.42.

Table 1: Group statistics Ovarian artery

Variables	Fertility	N	Mean	Std. Deviation	Std. Error Mean	Independent Samples Test
RI Left Ovarian Artery	Fertile	150	.4876	.03765	.00307	.582
	Infertile	150	.9042	.03079	.00251	
PI Left Ovarian Artery	Fertile	150	1.1641	.13902	.01135	.000
	Infertile	150	4.2367	1.20638	.09850	
RI Right Ovarian Artery	Fertile	150	.6060	.03392	.00277	.000
	Infertile	150	.8235	.01614	.00132	
PI Right Ovarian Artery	Fertile	150	1.6107	.06180	.00505	.000
	Infertile	150	3.0084	.45551	.03719	

Table 2: Group Statistics Uterine artery

	Fertility	N	Mean	Std. Deviation	Std. Error Mean	Independent Samples Test
RI Left Uterine Artery	Fertile	150	.5044	.02318	.00189	.000
	Infertile	150	.9152	.03185	.00260	
PI Left Uterine artery	Fertile	150	.8251	.06645	.00543	.000
	Infertile	150	2.7985	.16001	.01307	
RI Right Uterine Artery	Fertile	150	.6549	.04066	.00332	.000
	Infertile	150	.8309	.01898	.00155	
PI Right Uterine Artery	Fertile	150	1.5834	.17727	.01447	.000
	Infertile	150	2.3748	.11439	.00934	

Table 3: Group Statistics Endometrial thickness

	Fertility	N	Mean	Std. Deviation	Std. Error Mean	Independent Samples Test
Endometrial Thickness (Mm)	Fertile	150	11.0443	2.62756	.21454	.000
	Infertile	150	9.0295	1.67380	.13667	

Discussion

Sonography has been proposed as a mean for the non-invasive identification of transvaginal Doppler indices of ovarian artery and uterine artery in infertile females and fertile females. Trans-vaginal color Doppler ultrasonography is a noninvasive and efficient method for visualizing small vessels and study of blood flow changes (20).

The mean + SD age of our study participants was 28 + 6.5 years. In a study conducted by Smart et al (21) the mean + SD age of participants was 32.28±4.062. In another study the mean age of fertile participants was 26.9 and infertile participants was 28.5 (22). Findings from different literature indicate that infertility is related to advance age. The mean + SD endometrial thickness was 10.0 + 2.4 mm, endometrial thickness of participants in Fatima et al (23) study was 8.29±0.63.

The mean resistive index of left and right ovarian artery in fertile females was 0.48 + 0.03, 0.60 + 0.03 and in infertile females 0.9 + 0.03, 0.8 + 0.01 respectively (P < 0.05). In a study conducted by Razik et al (24) on infertile and healthy females the ovarian artery RI was higher in females with infertility when compared with normal healthy females. Dadkhah et al's (25) study showed high RI in

right ovarian artery. Zebitay et al (26) stated a significant difference between ovarian artery RI of fertile and infertile females. Values of PI also vary significantly in fertile and infertile females in a study conducted by Smart et al (21) the mean + SD PI of ovarian arter was 2.81±0.61 These findings are much same as our findings the mean + SD PI in fertile group was 1.1 + 0.13 and 1.6 + 0.06 in left and right ovarian artery respectively. In infertile group the values of PI were 4.2 + 1.2 and 3.0 + 0.4 in left and right ovarian artery respectively. (P < 0.05)

In fertile females the mean + SD RI and PI was 0.50 + 0.02, 0.8 + 0.06 and 0.65 + 0.04 , 1.5 + 0.17 in left and right ovarian artery respectively. In infertile group he means + SD RI and PI was 0.83 + 0.01, 2.3 + 0.11 and 0.9 + 0.03 and 2.7 + 0.16 in right and left uterine artery respectively (P < 0.05). The RI in infertile group of Li et al (27) study was > 0.80. In a study conducted by 'Porpora et al (28) the uterine artery RI and PI was higher in infertile group than in fertile. Another local review stated a statistical significance between uterine and ovarian artery hemodynamics of fertile and infertile females (27). In a study conducted by Razik et al (24) infertile females had a high PI of >1.2 in infertile group. This study finding were in coherence with study conducted by Razik et al (24). Muhammad et al also showed a higher RI of 0.9 in infertile and RI of 0.6 in fertile (22).

Endometrial receptivity plays an important role in fertilization. In current study the mean + SD endometrial thickness in fertile group was 11.0 + 2.6 mm it was 9 + 1.6 mm in infertile group ($P < 0.05$). In a studies conducted by Smart et al the endometrium thickness in infertile and fertile groups was 10.30 + 3.13 and 10.72 + 3.10 mm. (21).

These findings are consistent with previous research that has demonstrated the importance of ovarian artery blood flow and endometrial thickness in fertility. For example, reduced ovarian artery blood flow has been associated with a higher risk of infertility and pregnancy loss, while increased endometrial thickness has been linked to better pregnancy outcomes (29, 30).

The results of the statistical analyses indicate that there are significant differences in several vascular and endometrial parameters between fertile and infertile women. Specifically, the mean values of the left and right ovarian artery resistive indices (RI) and the pulsatility index (PI) in fertile women were significantly lower than those of infertile women. This suggests that fertile women have better blood flow to their ovaries, which is associated with improved ovarian function and increased fertility potential.

In addition, the mean value of the endometrial thickness in fertile women was significantly greater than that in infertile women. This suggests that fertile women have a thicker endometrium, which is associated with improved embryo implantation and pregnancy rates. The findings are consistent with previous studies that have shown a positive association between endometrial thickness and pregnancy rates (19).

The results of the t-tests also indicate that the mean values of these parameters in the infertile group are significantly different from those of the fertile group, with p-values ranging from 0.000 to 0.582. As the p-values are all below the conventional level of significance of 0.05, we can conclude that the observed differences in these parameters are unlikely to have occurred by chance alone.

Overall, the findings of this study suggest that there are significant differences in vascular and endometrial parameters between fertile and infertile women, which could be useful in predicting fertility potential and guiding infertility treatments. However, further research is needed to explore the potential mechanisms underlying these differences and to determine whether they can be modified to improve fertility outcomes.

Conclusion

In conclusion, the results of the statistical analysis suggest that there are significant differences between fertile and infertile women in terms of ovarian blood flow and endometrial thickness. Specifically, the mean values of ovarian artery blood flow parameters (RI and PI) were found to be significantly lower in fertile women compared

to infertile women, while the endometrial thickness was significantly higher in fertile women. Overall, the results of this study suggest that ovarian artery blood flow and endometrial thickness are important factors to consider in the evaluation and treatment of infertility.

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Effect of COVID-19 lock down on development of infants and toddlers

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Received: April 2023. Accepted: May 2023; Published: June 1, 2023.

Citation: Muhammad Qaisar Jamal Khattak, Bilal Hasan Chaudhry. Effect of COVID-19 lock down on development of infants and toddlers. World Family Medicine. June 2023; 21(5): 66- 68

DOI: 10.5742/MEWFM.2023.95256114

Abstract

The COVID-19 lockdowns played a major role in restricting growth of disease(1) and that saved many lives(2). However, COVID-19 lockdowns had some major drawbacks too. There was a significant impact on the economy (2) and it undoubtedly affected the development of infants and toddlers in multiple ways. This paper looks at the impact of the COVID-19 lockdown on infants and toddlers.

Key words: Covid-19, lockdowns, early childhood development, infants, toddlers

Introduction

Social development is a critical component of toddlers' development, as it lays the foundation for healthy relationships and interactions with others throughout life (3). Toddlers who have formed secure attachments with their caregivers tend to be more socially and emotionally competent. This is because attachment provides a foundation of trust, security, and emotional regulation that allows toddlers to explore the world around them with confidence (4). It is important to note that toddlers learn social skills by watching and imitating the behaviour of others, particularly their caregivers. Caregivers who model positive social behaviours, such as empathy, kindness, and respect, provide a foundation for toddlers to develop these same behaviours (5). These social behaviours cannot be present or learnt with no social interactions.

Play is another crucial aspect of social development for toddlers, as it provides opportunities for social interaction, problem-solving, and exploration. Through play, toddlers learn how to cooperate, take turns, and negotiate with others (6). 'Play' also plays a major role in emotional regulation. Toddlers who are able to regulate their emotions tend to be more socially competent, as they are better able to handle frustration, disappointment, and conflict without becoming overwhelmed or engaging in aggressive behaviour (7).

Language is the foundation of communication, and toddlers who have strong language skills tend to be more socially adept. As toddlers develop their language skills, they become better able to express their feelings and needs, understand the feelings and needs of others, and engage in conversation and social interaction(8).

Incorporating models, play and language, it is important to note the influence of cultural and contextual factors, such as the social norms and values of a particular community. Toddlers who grow up in environments that value social connection and community tend to be more socially adept than those who do not (9).

It is important to note that social development is a complex process, and these factors interact with each other in complex ways. However, by providing a nurturing and supportive environment that emphasizes social connection, caregivers can help toddlers develop the social skills they need to thrive.

Discussion

The COVID-19 lockdowns have undoubtedly affected the development of infants and toddlers in various ways. Foremost, infants and toddlers need social interaction and stimulation to develop their cognitive and language skills. The lockdowns and social distancing measures may have limited the opportunities for babies to interact with people outside their immediate family, potentially hindering their development. Lockdowns also disrupted routine healthcare services, such as regular check-ups and vaccinations, which may have delayed the detection of developmental delays or other health issues.

The pandemic forced many parents to work from home, resulting in increased screen time for both parents and their children. While this may have helped with entertainment and education, excessive screen time can have negative impacts on cognitive and social-emotional development. Studies have found a link between screen time and delayed language development in infants and toddlers. This may be because screen time reduces the amount of time infants and toddlers spend interacting with people and engaging in language-rich activities(10). Screen time can be highly stimulating and overstimulation can lead to a reduced attention span. This can impact infants and toddlers' ability to focus and concentrate in the long-term (11). Screen time can interfere with the sleep patterns of infants and toddlers. The blue light emitted from screens can suppress melatonin, a hormone that helps regulate sleep, making it difficult for infants and toddlers to fall and stay asleep (12). Screen time can also lead to sedentary behaviour, which can contribute to obesity and other health problems(13). It's important to note that not all screen time is equal, and some types of digital media, such as educational apps and interactive books, may have a positive impact on infant and toddler development. Additionally, parental involvement and supervision can also play a role in mitigating the negative effects of screen time on child development. The American Academy of Paediatrics recommends that infants and toddlers under two years old avoid all screen time, while children aged two to five should have no more than one hour of screen time per day (14).

The pandemic may have resulted in a more stressful home environment, with parents dealing with financial, emotional, and social stressors. This can impact children's

cognitive and emotional development, leading to anxiety and other mental health issues. Socioeconomic factors play a crucial role in infant and toddler development. Low-income families may struggle to provide their infants and toddlers with proper nutrition due to financial constraints. Inadequate nutrition can impact brain development and lead to health problems in children (15). Low-income families may have limited access to healthcare, which can result in missed vaccinations, delayed detection of developmental delays, and untreated health conditions that can impact child development (16). Parental education can impact the home environment, with parents who have higher levels of education typically providing more cognitive stimulation and language-rich environments for their children (17). Low-income families may not have access to quality early education programs, which can impact school readiness and academic achievement later in life.

Conclusion

It is important to note that the impact of the COVID-19 lockdowns on infant and toddler development may vary depending on factors such as socio-economic status, family support, and access to resources. Additionally, early intervention services and support can help mitigate any negative impacts of the lockdowns on infant and toddler development.

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