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Hypovitaminosis E and Endometriosis in a Sub-Saharan Population

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Abstract

Endometriosis is a chronic gynecological condition defined by the presence of endometrial-like tissue outside the uterus affecting approximately one in 10 women worldwide. Endometriosis is source of chronic pelvic pain and infertility and represents a significant economic burden. This study aims to determine the frequency of hypovitaminosis E in sub-Saharan women in Kinshasa with endometriosis and identify associated risk factors. A case-control study of 244 patients undergoing a laparoscopy in 8 Kinshasa medical centers between January 2019 and October 2022. Among these, 82 women with endometriosis (cases) and 164 women with a normal pelvis (controls) were matched in age function. Chi-square tests and t-tests were used to compare these two groups. A multivariate logistic regression was performed to identify risk factors related to endometriosis. Hypovitaminosis E in women with endometriosis was 74.39%. Dysmenorrhea (OR 24.234 [95% CI: 12.141 - 50.026)], $p < 0.001$), nulliparity (OR 5.157 [95% CI: 2.458 - 10.819], $p < 0.001$), history of unsafe abortion (OR 8.389 [95% CI: 4.277 - 16.476], $p < 0.001$), infertility (OR 5.157 [95% CI: 2.458 - 10.819], $p = 0.02$), early menarche (OR 28.830 [95% CI: 13.640 - 60.933], $p < 0.001$) and hypovitaminosis E (OR 4.538 [95% CI: 2.523 - 8.161], $p < 0.001$ were identified as risk factors. Use of oral contraceptives (OR 0.188 [95% CI: 0.093 - 0.381], $p < 0.001$) had a protective factor against endometriosis. Despite some limits, our data underline the role of vitamin E deficiency as a potential factor of endometriosis in a

sub-Saharan population especially subject to deficiency intake.

Subject Areas

Gynecology & Obstetrics

Keywords

Endometriosis, Risk Factors, Sub-Saharan Women, Hypovitaminosis E, Unsafe Abortion

1. Introduction

Endometriosis is an estrogen-dependent chronic pelvic inflammatory disease characterized by the implantation and growth of endometrial tissue (glands and stroma) outside the uterus [1] [2] [3]. Endometriosis affects approximately 10% - 15% of women of childbearing age [4] [5]. The most common symptoms of the disease are pelvic pain, dysmenorrhea and infertility [1] [2] [3] [4] [5]. However, endometriosis can also be asymptomatic [5] [6] [7].

The etiology of endometriosis is still poorly understood [8]-[14]. Several studies have shed light on the role of factors in the development of endometriosis such as familiar tendency, genetic predisposition, epigenetics, immune system dysfunction as well as oxidative stress [2] [8] [9] [10] [15] [16] [17] [18] [19]. It is now widely accepted that oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and antioxidants, may be involved in the pathophysiology of endometriosis causing a general inflammatory response in the peritoneal cavity [17] [18] [19]. ROS are intermediates produced by normal oxygen metabolism and are inflammatory mediators known to modulate cell proliferation and have deleterious effects [20]. An excess of free radicals or an antioxidant deficit can cause oxidative stress and thus contribute to the development of certain inflammatory diseases including endometriosis [17] [18] [19] [20]. Indeed, oxidative stress and inflammation are closely linked processes: free radicals promote inflammation via inflammatory mediators (e.g. pro-inflammatory cytokines and prostaglandin 2), and inflammation causes the production of free radicals [10] [13] [21] [22]. Several studies have shown increased oxidative stress in the serum and peritoneal fluid of endometriotic women [14] [20]. An increase in oxidative stress has been shown in epithelial cells derived from ovarian endometriomas, secondary to an increase in the production of ROS and a lack of detoxification [23]. Moreover, this has been confirmed in vivo on mouse models of endometriosis treated with an antioxidant, N-acetyl-cysteine, which allows not only the reduction of endometriotic implants but also the decrease in local inflammatory phenomena [23]-[30]. Among the various antioxidant (enzymatic and non-enzyme), such as superoxide dismutase, catalase and glutathione peroxidase [24] [26], vitamin E (neutralizing hydrogen peroxide) can play a crucial role by limiting the produc-

tion of ROS, inactivating them and contributing to repair cell damage.

Vitamin E has received a lot of attention in recent years for its ability to improve reproductive health [31] [32] [33]. Moreover, vitamin E is involved in a wide range of physiological processes, from immune function and inflammation control to the regulation of gene expression and cognitive performance [33]. Vitamin E deficiency is a global public health concern [34] [35]. It is estimated that 2 billion people worldwide suffer from micronutrient deficiencies, especially pronounced in Africa [36]. Several epidemiological studies have shown that supplementation with a trace element, including vitamin E, considerably reduces the symptoms associated with endometriosis and improves the quality of life of endometriosis women [37] [38] [39] [40].

Therefore, the aim of the present case-control study was to determine the frequency of hypovitaminosis E in sub-Saharan women with endometriosis in Kinshasa.

2. Materials and Methods

2.1. Materials

The patients included in the present case control study were recruited from eight hospitals in the City of Kinshasa: African Union Presidential Clinic (CPUA), Onyx Medical Center (OMC), University Clinics of Kinshasa (CUK), Edith Medical, HJ Hospital, Clinique Diamant, Clinique Medecin de Nuit and Clinique Dr. Lipombi, from January 1, 2019 to October 30, 2022.

All the patients included were black and of Congolese nationality. The information was collected using a data collection sheet including questions on the demographic, clinical, paraclinical and surgical characteristics of the patients. All the patients had an indication for laparoscopy (diagnostic or operative) based on symptoms of endometriosis (dyspareunia, dysmenorrhea and pelvic pain) or infertility workup. Our case-control study consisted of one case for two controls, ie 82 cases and 164 controls. Our cases and controls were age-matched. Cases were defined by the presence of endometriotic lesions visible at laparoscopy and confirmed by histology. Controls were women with a normal pelvis at laparoscopy. Were excluded any patient with peritonitis, adhesions without evidence of endometriosis and cases of gynecological cancer. All the surgeons involved in the study are experienced in identifying the different forms of lesions and in the surgical management of endometriosis.

The stage of the disease was defined according to the classification system of the American Society for Reproductive Medicine: Stage I (minimal), Stage II (mild), Stage III (moderate) and Stage IV (severe) [41].

2.2. Methods

Vitamin E dosage was performed by venous blood collected from the participants in the morning after 8 - 12 h of overnight fasting. Samples were centrifuged and the serum separated from the blood cells, aliquoted, then frozen below

−20˚C. A set of samples was addressed to the Molecular Medicine Laboratory of the Biomedical Research Institute (IRB) of the Training and Health Support Center (CEFA) MONKOLE/DR Congo, where serum vitamin E has been analyzed.

Serum vitamin E determination was evaluated using an enzyme-linked immunoassay (ELISA) sandwich method (Mybiosource Ltd. USA) and an Elisa Micro Plate Reader plate analyzer from Inqaba Biotech, Inqaba Biotechnical Industries (Pty Ltd. Pretoria, South Africa) in accordance with the manufacturer's instructions. A micro-Elisa strip plate provided in the kit was pre-coated with an antibody specific to vitamin E standards. A specific vitamin E conjugate to horseradish peroxidase (HRP) was added to each micro-Elisa strip plate well and incubated. 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution was added to each well. Only wells containing vitamin E and HRP-conjugated anti-vitamin E antibodies appeared blue in color, then turned yellow after addition of Stop Solution.

Spectrophotometric optical density (OD) was measured at a wavelength of 450 nm. The OD value is proportional to the vitamin E concentration. The vitamin E concentration in the samples was calculated relative to the OD of the samples on the curve. We used 4.52 to 14.64 mg/L as a reference value in women of childbearing age. Any concentration lower than 4.52 mg/L was considered as hypovitaminosis (*α*-tocopherol) [42].

The study was approved by the Ethics Committee of the School of Public Health of the University of Kinshasa according to the Declaration of Helsinki. Our Data were analyzed using STATA 17.0 software. Quantitative variables were expressed as mean ± standard deviation (normally distributed variables), median and interquartile range (non-normally distributed variables); qualitative variables as absolute and relative frequencies (in percentage). The comparison of the means and medians of two groups was made using Student's and Mann-Whitney's t-tests respectively. The comparison of proportions was made using the Chi Square Test. A multivariate logistic regression was performed in which all studied associations (ORs), along with 95% confidence intervals (CIs), were estimated to indicate the strength of these associations with $p \leq 0.05$.

3. Results

3.1. Sociodemographic and Clinical Characteristics of the Study Population

In our series, the frequency of endometriosis at laparoscopy was 19.1%. The age of our patients was between 20 and 47 years-old with a mean age of 33.1 ± 6.9 years. Sociodemographic and clinical characteristics of the patients are summarized in Table 1.

3.2. Distribution of serum Vitamin E

Figure 1 shows the serum distribution. The means and standard deviation as well as the reference intervals of vitamin E in the endometriosis and control groups are given in Table 2. Two-third of the endometriosis population had a

Table 1. Sociodemographic and clinical characteristics of patients.

Variables	Endometriosis		p
	Yes (n = 82)	No (n = 164)	
BMI			0.830
<25	69 (84.1)	112 (68.3)	
≥25 - <30	5 (6.0)	28 (17.1)	
≥30	8 (9.9)	24 (14.6)	
Profession			0.733
Employed	65 (79.0)	133 (81.1)	
Not employed	17 (21.0)	31 (18.9)	
Marital status			0.465
Maried	50 (61.0)	92 (56.1)	
Singles	32 (39.0)	72 (43.9)	
Educational level			0.472
Secondary	19 (23.0)	45 (27.4)	
University	63 (76.83	119 (72.6)	
Patients with dyspareunia	29 (35.0)	57 (35.0)	0.041
Patients with dyschesia	6 (7.0)	31 (19.0)	0.102
Patients with voiding dysfunction	18 (22.0)	90 (55.0)	0.721
Patients with metrorrhagia	37 (45.0)	71 (43.0)	0.020
Patients with chronic pelvic pain	17 (21.0)	65 (40.0)	0.612
Patients with dysmenorrhea	68 (83.0)	26 (16.0)	0.001
Oral Contraception	11 (13.0)	74 (45.0)	0.001
Intra Uterine Device	8 (10.0)	4 (4.0)	0.052
Ysmenorrhea > 7 on VAS	33 (39.8)	93 (56.7)	0.051
Prior abdominal surgery	18 (21.4)	73 (44.8)	0.062
Infertility	32 (39.0)	74 (45.1)	0.019
Parity			0.001
Nulliparous	13 (15.8)	49 (29.9)	
Primiparous	52 (63.4)	38 (23.2)	
Multiparous	17 (20.8)	77 (46.9)	
Spontaneous abortion	16 (19.5)	40 (24.4)	0.390
Unsafe abortion	39 (47.6)	16 (9.8)	0.001
Menarche (years)			0.001
≤12	71 (86.6)	30 (18.3)	
≥13	11 (13.4)	134 (81.7)	
Menstrual cycle			0.047
Regular	31 (37.8)	84 (51.2)	
Irregular	51 (62.2)	80 (48.8)	
Duration of menstruation (day)			0.020
≤7	34 (41.2)	117 (71.1)	
≥8	48 (58.8)	47 (28.9)	

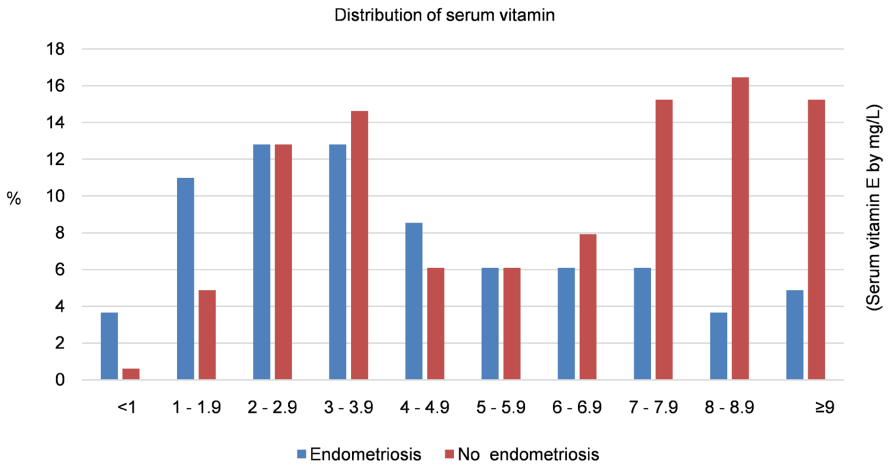

Figure 1. Distribution of serum vitamin E in both endometriosis and controls groups (p = 0.001).

Table 2. Mean and reference interval of serum vitamin E in both endometriosis and controls groups.

Vitamin E (mg/L)	Endometriosis		Endometriosis
	Yes (n = 82)	Yes (n = 82)	
Mean ± standard deviation	4.80 ± 3.3	6.25 ± 4.3	0.023
Reference Interval			0.001
Hypovitaminosis (<4.52)	54 (65.9)	83 (50.6)	
Normovitaminosis (≥4.52)	28 (34.6)	81 (49.4)	

hypovitaminosis that was higher to the non-endometriosis group (p = 0.001).

3.3. Characteristics at Laparoscopy

Laparoscopic findings (Table 3) in both: case and control groups were dominated by the presence of myomas (15.8% and 28.6%) and tubal obstruction (10.9% and 20.7%). According to the endometriosis phenotype, the superficial peritoneal phenotype was the most prevalent (29.2%) followed by endometrioma (21.6%) and deep endometriosis (19.3%).

Among patients with endometriosis, the main surgical procedure was electrocoagulation of the lesions (about one third of the population) raising the issue on the risk of recurrence. In addition, ovarian cystectomy was performed in one quarter of the endometriosis population with potential negative impact on ovarian reserve. Finally, we noted that two-third of the endometriosis population exhibited III-IV rASRM stages.

3.4. Univariable and Multivariable Analysis

To evaluate the relationship between socio-epidemiological characteristics, paraclinical, (including hypovitaminosis E dosage) and laparoscopic findings univariate (crude Odd Ratio) and multivariate (adjusted Odd Ratio) analysis was

Table 3. Surgical characteristics in both endometriosis and controls groups.

Variables	Endometriosis	
	Yes (n = 82)	No (n = 164)
Laparoscopic finding		
Normal pelvis	0 (0.0)	17 (10.4)
Uterine myomas	13 (15.8)	47 (28.6)
Uterine hypoplasia	0 (0.0)	7 (4.3)
Ovarian cysts no endometriosis	0 (0.0)	29 (17.7)
Micro polycystic ovary	0 (0.0)	11 (6.7)
Ectopic pregnancy	0 (0.0)	11 (6.7)
Fitz Hugh Curtis syndrome	0 (0.0)	8 (4.9)
Tubal obstruction	9 (10.9)	34 (20.7)
Endometriosis	82 (100.0)	0.00
Endometriosis Phenotypes		
Superficial peritoneal endometriosis	24 (29.2)	-
Endometrioma	18 (21.6)	-
Deep endometriosis	16 (19.3)	-
Endometrioma and deep pelvic	11 (13.6)	-
Peritoneal, deep pelvic endometriosis	13 (16.3)	-
Laparoscopic procedures		
Electro-coagulation of peritoneal lesion	29 (35.3)	-
Salpingectomy	8 (9.7)	-
Unilateral ovarian cystectomy	10 (12.1)	-
Bilateral ovarian cystectomy	13 (15.8)	-
Torus resection	5 (6.0)	-
Uterosacral ligament resection	8 (9.7)	-
Ureterolysis	2 (2.4)	-
Colpectomy	3 (3.7)	-
Bowel resection	4 (4.8)	-
rASRM stage (Laparoscopy)		
I and II	30 (36.59)	-
III and IV	52 (63.41)	-

performed (Table 4).

Among the most relevant characteristics associated with endometriose were, early menarche (OR 28.830 [95% CI: 13.640 - 60.933], $p < 0.001$), dysmenorrhea considering the intensity according to the visual analogue scale ≥ 7 (OR 24.234 [95% CI: 12.141 - 50.026], $p < 0.001$), history of unsafe abortion (OR 8.389 [95% CI: 4.277 - 16.476], $p < 0.001$), nulliparity (OR 5.157 [95% CI: 2.458 - 10.819],

Table 4. Relation between socio-epidemiological characteristics, serum level of E vitamin and the presence of endometriosis.

Variables	Univariable analysis OR (95% CI)	p	Multivariable analysis OR (95% CI)	p
Parity				
Nulliparous	4.157 (2.458 - 12.889)	<0.001	5.157 (2.458 - 10.819)	<0.001
Primiparous	0.132 (0.471 - 1.891)	0.655	0.832 (0.371 - 3.861)	0.655
Multipara	1		1	
Spontaneous abortion	0.611 (0.491 - 1.492)	0.390	0.751 (0.391 - 1.442)	0.390
Unsafe abortion	7.319 (4.277 - 15.476)	<0.001	8.389 (4.277 - 16.476)	<0.001
Menarche				
≥13 years old	1		1	
≤12 years	26.870 (8.640 - 62.913)	<0.001	28.830 (13.640 - 60.933)	<0.001
Dysmenorrhea	25.434 (11.144 - 55.021)	<0.001	24.234 (12.141 - 50.026)	<0.001
Abdominal surgery	2.127 (1.458 - 6.819)	<0.000	0.157 (0.458 - 2.819)	0.610
Secondary infertility	1.830 (1.107 - 3.260)	0.021	1.900 (1.107 - 3.260)	0.020
Dyspareunia	1.637 (1.347 - 8.754)	<0.001	0.617 (0.347 - 2.754)	0.715
Dyschesia	2.134 (1.006 - 5.996)	0.016	0.134 (0.006 - 2.996)	0.205
Dysuria	1.971 (1.304 - 5.468)	0.041	0.571 (0.304 - 1.468)	0.671
Metrorrhagia	0.726 (0.547 - 1.803)	0.231	0.726 (0.547 - 1.803)	0.231
Chronic Pelvic Pain	1.314 (1.082 - 5.090)	0.027	0.754 (0.082 - 2.090)	0.783
Oral contraception	0.418 (0.093 - 0.981)	<0.001	0.188 (0.093 - 0.381)	<0.001
Intra-uterine device	1.615 (1.326 - 5.323)	0.013	0.655 (0.326 - 1.313)	0.233
Hypovitaminosis E	3.538 (2.823 - 8.241)	<0.001	4.538 (2.523 - 8.161)	0.023

$p < 0.001$), hypovitaminosis E (OR 4.538 [95% CI: 2.523 - 8.161], $p < 0.001$) and secondary infertility (OR 1.900 [95% CI: 1.107 - 3.260], $p = 0.020$). On the other hand, the use of oral contraceptives (OR 0.188 [95% CI: 0.093 - 0.381], $p < 0.001$) was happened to be a protective factor against endometriosis.

To evaluate the relation between socio-epidemiological, serum (including hypovitaminosis E) and surgical characteristics and the presence of endometriosis, a univariate (crude Odd Ratio) and multivariate (adjusted Odd Ratio) analysis was performed (Table 4).

Among the most relevant epidemiological and surgical characteristics, early menarche (OR 28.830 [95% CI: 13.640 - 60.933], $p < 0.001$), dysmenorrhea considering the intensity according to the visual analogue scale ≥ 7 (OR 24.234 [95% CI: 12.141 - 50.026)], $p < 0.001$), history of unsafe abortion (OR 8.389 [95% CI: 4.277 - 16.476], $p < 0.001$), nulliparity (OR 5.157 [95% CI: 2.458 - 10.819], $p < 0.001$), hypovitaminosis E (OR 4.538 [95% CI: 2.523 - 8.161], $p < 0.001$) and secondary infertility (OR 1.900 [95% CI: 1.107 - 3.260], $p = 0.020$). On the other hand, the use of oral contraceptives (OR 0.188 [95% CI: 0.093 - 0.381], $p < 0.001$) proved to be a protective factor against endometriosis.

4. Discussion

The present case-control study, with multivariable analysis, demonstrates the relation between hypovitaminosis E and lalaroscopic diagnosis of endometriosis in a sub-Saharan population with an OR: 4.538 (95% CI: 2.523 - 8.161, $p < 0.001$). Moreover, more than a quarter of case group had a severe hypovitaminosis E (inferior to 3 mg/L). Our findings are consistent with those of Murphy *et al.* [43] who, first, highlighted the role of oxidative stress in the pathogenesis and development of endometriosis. Subsequently, several studies have confirmed the relation between low level of vitamin E and endometriosis [44] [45]. Moreover, Darling *et al. [46]* reported among 1383 incident cases of laparoscopically-confirmed endometriosis that vitamin E level was inversely associated with endometriosis (OR = 0.70; 95% CI: 0.59 - 0.83; $p < 0.001$). However, data of the current study must be analyzed with caution particularly in the sub-Saharan population. First, vitamin E deficiency is a global public health concern especially in developing countries [34] [35]. It is estimated that 2 billion people worldwide struggle with micronutrient deficiencies, and this is most acute in Africa [36] [47] [48] [49] [50] [51]. Moreover, there is a lack on the true incidence and prevalence of endometriosis in Africa not permitting to draw definitive conclusion on vitamin E deficiency and endometriosis [52]. Indeed, inadequate micronutrient intake is also an issue in people of childbearing age [53]-[58]. Results from several studies reveal that poor nutritional status and higher prevalence of other oxidative stressors such as malaria and HIV infection predispose populations in developing countries to vitamin E deficiency [32] [33] [34] [56]. This deficiency is associated with increased prevalence of infections, anemia, stunted growth, and might be a factor of endometriosis development [34] [35]. Second, vitamin E is a collective term that refers to all tocol and tocotrienol derivatives including four tocopherols and four tocotrienols that share the chromanol ring structure [57] [58]. Among them, α-tocopherol is selectively enriched in human tissues inhibiting lipid peroxidation caused by oxidative stress [59]. Finally, the cut-off used to define vitamin E deficiency varies widely according to populations, from 2.8 to 24 µmol/L (0.1 to 1.0 mg/dL) for serum α-tocopherol [60].

Beyond the relation between hypovitaminosis E and the diagnosis of endometriosis, we observed a relation with some symptoms suggestive of endometriosis. Using univariable analysis, a relation was observed between hypovitaminosis E and dysmenorrhea, dyspareunia, dyschesia, dysuria and chronic pelvic pain but on multivariable analysis the relation was only confirmed for dysmenorrhea (OR: 24.234, 95% CI: 12.141 - 50.026, $p < 0.001$). When considering the intensity of dysmenorrhea between patients with and without endometriosis, a difference was observed between the groups, but only a trend for severe dysmenorrhea over 7 on VAS? The identification of oxidative stress as a major factor in endometriosis has prompted several authors to investigate the potential therapeutic action of vitamin E supplementation to reduce oxidative stress. Several randomized tri-

als have looked at the effects of vitamins E and C in women with endometriosis-related pain. Women supplemented with Vitamin E experienced a reduction in pain, even in the short term [38]. Santanam *et al.* attributed the effects of vitamin E supplementation to its antioxidant and anti-inflammatory properties, although they described no clear physiological mechanism underlying this effect [40]. However, the 2016 Cochrane review on dietary supplements for dysmenorrhea versus placebo or no treatment stated no evidence of effectiveness for vitamin E. In a randomized double-blind trial, Mier-Cabrera *et al.* evaluated the impact of vitamins C and E supplementation on malondialdehyde (MDA) and lipid hydroperoxides (LOOH) serum levels as biomarkers of oxidative stress. They found a significant decrease in MDA and LOOH levels after 4 and 6 months of supplementation [24]. Since the publication of the Cochrane review, recent randomized trials and literature review have demonstrated the therapeutic action of vitamin E supplementation [38] [61] [62]. Despite no significant decline in total antioxidant capacity, the effectiveness of vitamin E supplementation on severity of pelvic pain ($p < 0.001$), dysmenorrhea ($p < 0.001$), and dyspareunia ($p < 0.001$) was noted suggesting that additional unknown co-factors to vitamin E are probably implicated in the therapeutic action [61].

From physiopathology point of view of endometriosis, vitamin E has proved its role as antioxidant and free radical scavenger, protecting the integrity of unsaturated lipids in the bio-membranes of cells [32] [56]. Van Langendonckt *et al.* described a positive correlation between preventing the onset of endometriosis in rabbits and the increase in antioxidant levels. They also found higher levels of release of reactive oxygen species from macrophages, higher peritoneal levels of oxidized low-density lipoproteins and their byproducts, altered expression of endometrial antioxidant enzymes and decrease in vitamin E in peritoneal fluid [27]. Retrograde menstruation appears to be associated with highly pro-oxidant factors *i.e.* heme and iron in the peritoneal cavity, in addition to apoptotic endometrial cells known to induce oxidative stress [27] [43]. Moreover, vitamin E is involved in a wide range of physiological processes, from immune function and control of inflammation to regulation of gene expression, cognitive performance, and oxidation sensitive nociception involved in endometriosis [32] [33] [44] [45] [56]. Patients with endometriosis appear to have higher lipid peroxidase levels and lower selenium, superoxide dismutase and vitamin E levels than healthy controls; therefore, the reduction of the antioxidant system may be one of the underlying mechanisms in the occurrence of endometriosis [63].

Some limits of the present study deserve to be underlined. First, despite the use of a case control methodology, it is not possible to exclude biases related to the characteristics of the study population. Second, the sample size of patients with endometriosis remains relatively low representing a true limit. Third, we evaluated only the serum vitamin E level while other markers of oxidative stress (enzymatic and non-enzymatic) were not analyzed. Fourth, we do not evaluate the vitamin E-binding protein afamin that has been shown to be altered in

women with endometriosis imposing further studies [64].

5. Conclusion

In conclusion, the current study underlines the role of vitamin E deficiency as a potential factor of endometriosis in a sub-Saharan population. As previously claimed by Blaner [65], the functions, metabolism, and role of vitamin E is not fully elucidated and need further studies especially in the context of endometriosis.

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Conflicts of Interest

The authors declare no conflicts of interest.

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