Research Article ISSN 2639-9342

Gynecology & Reproductive Health

Comparison of Endoglin Levels (CD 105) in Women's Menstrual Blood Endometriosis and without Endometriosis

Jeimmy Mangalonggak, Nasruddin Andi Mappaware, St. Maisuri T. Chalid, John Rambulangi and Sharvianty Arifuddin

Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Hasanuddin, Dr. Wahidin Sudirohusodo General Hospital, Makassar.

***Correspondence:**
Jeimmy Mangalonggak, Department of Obstetrics and Gynecology, Faculty of Medicine Universitas Hasanuddin, Dr. Wahidin Sudirohusodo General Hospital, Makassar.

Received: 22 December 2020; **Accepted:** 05 January 2020

Citation: Jeimmy Mangalonggak, Nasruddin Andi Mappaware, St. Maisuri T. Chalid, et al. Comparison of Endoglin Levels (CD 105) in Women's Menstrual Blood Endometriosis and without Endometriosis. Gynecol Reprod Health. 2020; 4(1): 1-4.

ABSTRACT

Aimed: *To evaluate menstrual blood endoglin levels between women with endometriosis and without endometriosis.*

Methods: *A cross-sectional study was performed on 52 eligible women. Endometriosis was confirmed with laparoscopy or laparotomy. Menstrual blood collected in the first or the third day of menstrual cycle using a menstrual cup. Endoglin levels from menstrual blood serum were measured with the ELISA method.*

Results: *Menstrual blood endoglin levels in mild endometriosis were significantly higher compared with control (22.903 pg/ml vs 5.250 pg/ml; $p<0.05$) as well as the endoglin levels between severe endometriosis compared with mild endometriosis showed endoglin levels significantly higher in severe endometriosis (31.957 pg/ml vs. 22.903 pg/ml; $p<0.05$).*

Conclusion: Menstrual blood endoglin levels positively correlated with endometriosis stage.

Keywords

Endoglin, Endometriosis, Menstrual blood.

Introduction

Endometriosis generally found 6%-10% in women complaint with pain and infertility [1]. The incidence of endometriosis women with infertility ranging from 10%-70% and 50% in adolescents with complaints of dysmenorrhea [2]. Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity which causes chronic inflammation in the surrounding tissue leads to several symptoms including pelvic pain, dysmenorrhea, infertility, low back pain, dyspareunia, constipation, dysuria and diarrhea [3].

Several hypotheses have been put forward about the pathogenesis of the occurrence of endometriosis. The Sampson's theory proposed that menstrual blood can flow from the uterine cavity through the fallopian tubes to the pelvic cavity, adhesion, and growth. However, it cannot be explained why endometriosis occurs only in a small proportion of women. Most women experienced with retrograde menstruation (76-90%) into the peritoneal cavity but endometriosis occurs only 5-10% of women. There is an increase in retrograde menstruation in menstrual blood flow obstruction; ovarian endometriosis can be associated with retrograde menstruation or caused by lymphatic flow from the uterus to the ovary [4,5].

The major cause of endometriosis is unknown; however, there is evidence of involvement of immune, environmental and genetic factors. The genetic and hereditary factor were indicated about 5.3% of patients with endometriosis having a family history of endometriosis [6].

Functional endometrium consists of a layer of the columnar epithelium above the connective tissue layer. This connective tissue layer has a thickness varies according to hormonal influences - stroma. Simple tubular uterine glands reach the basal of the stroma through the endometrial surface, which also obtained blood from

the spiral arteries. Menstrual blood contains cells or tissue from the functional layer of the endometrium. This layer is formed after the end of the menstrual period.

Angiogenesis is the process of forming new blood vessels, originating from existing blood vessels. Angiogenesis in endometriosis leads to a significant increase of endoglin levels in serum and peritoneal fluid. Increased serum and peritoneal endoglin levels are associated with increased of endometriosis stages. The previous study showed serum endoglin levels and dysmenorrhea as predictors of higher endometriosis compared with serum endoglin levels and infertility. The combination of complaints of dysmenorrhea and cut-off of serum endoglin levels increases the positive predictive value >90% in endometriosis [7]. Other study show endoglin plays a role in the pathogenesis of endometriosis; endoglin found in peritoneal fluid and expressed in tissues that predict endometriosis [8].

Examination of endoglin levels in menstrual blood has the potential as a minimally invasive in diagnosing endometriosis and it has been used to diagnose dysfunctional uterine bleeding [9]. The present study aimed to evaluate menstrual blood endoglin levels between women with endometriosis and without endometriosis.

Methods

A cross-sectional study was conducted at Wahidin Sudirohusodo General Hospital and affiliated hospitals of Department of Obstetrics and Gynecology Medicine Faculty of Hasanuddin University Makassar from November 2017 to April 2018. Endometriosis was confirmed with laparoscopy or laparotomy. Women aged between 25 to 45 years, regular menstruation for the last 6 months, without any treatment for ovarian suppression using hormonal treatment for the last 6 months and not pregnant confirmed with ultrasound and laboratory examination were eligible. Women without endometriosis, malignancy and pelvic diseases as control.

Menstrual blood collected in the first or the third day of menstrual cycle using a menstrual cup. Endoglin levels from menstrual blood serum were measured using the enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions. Sample characteristics and the difference between study groups were tested using t-test. To evaluate the endoglin levels between endometriosis stages, the Kruskal-Wallis test was used. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Data were analyzed using SPSS version 23.0. The study approved by the Medical Research Ethics Committee of Hasanuddin University/ dr. Wahidin Sudirohusodo General Hospital No. Registry 153/ H4.8.5.31/PP36-KOMETIK/2017.

Results

Thirty women with endometriosis (n=27) and thirty women without endometriosis (n=25) were eligible for the study. Women for both groups were at the reproductive age (≤35 years). Compared with control, women in the study group has the similarity for parity and menstrual pain (dysmenorrhea) proportion. The characteristics of these women are shown in table 1.

Characteristics		Endometriosis (N=27)		Control (N=25)	
		n	%	n	%
Age (years)	≤35	25	92.6	24	96
	>35	2	7.4	1	4
Endometriosis stages	I/II (mild)	10	37		
	III/IV (severe)	17	63		
Education (years)	<9	17	63	15	60
	≥9	10	37	10	40
Parity	Nulliparity	16	59.3	3	12
	Multiparity	11	40.7	22	88
Infertility	Yes	17	63	3	12
	No	10	37	22	88
Dymenorrhea	Yes	15	55.6	4	16
	No	12	44.4	21	84

Table 1: Baseline characteristics of the subgroups.

The endoglin levels in menstrual blood from 52 women showed significantly different ($p<0.05$) based on parity, infertility, dysmenorrhoea, and endometriosis stage (Table 2).

Variables		Endoglin levels		P	OR (95%CI)
		High (> 11 pg/ml)	Low (≤11 pg/ml)		
Age (years)	≤ 35	26 (92.2)	23 (95.8)	1.000	0.565 (0.048-6.650)
	> 35	2 (7.1)	1 (42.2)		
Parity	Nulliparity	16 (57.1)	3 (12.5)	0.001	9.333 (2.250-38.711)
	Multiparity	12 (42.9)	21 (87.5)		
Infertility	Yes	17 (60.7)	3 (12.5)	<0.001	10.818 (2.595-45.101)
	No	11 (39.3)	21 (87.5)		
Dysmenorrhea	Yes	15 (53.6)	4 (16,7)	0.006	5.769 (1.564-21.283)
	No	13 (46.4)	20 (83.3)		
Endometriosis stage	Not endometriosis	1 (3.6)	24 (100)	< 0.001	
	Mild	10 (35.7)	0		
	Severe	17 (60.7)	0		

Table 2: Endoglin levels based on clinical variables.

Table 3 shows the comparison of endoglin levels based on endometriosis stage. There was a significant difference between menstrual blood endoglin levels in mild endometriosis compared with controls. The endoglin levels were significantly higher in mild endometriosis compared with control [22.903 pg/ml vs. 5.250 pg/ml]. The similarity also found in the endoglin levels of menstrual blood between severe endometriosis compared with mild endometriosis that the endoglin levels were higher in severe endometriosis compared with mild stage [31.957 pg/ml vs. 22.903 pg/ml; $p<0.05$] (Table 3).

Sample	n	Endoglin levels (mean ±SD pg/ml)	p
Stage			
Mild	10	22.903 ± 7.328	0.002
Severe	17	31.957 ± 4.910	
Control	25	5.250 ± 1.870	

Table 3: Endoglin levels and endometriosis stage.

Discussion

The present found higher levels of endoglin in menstrual blood endometriosis patients compared with without endometriosis. The previous study on the relationship of angiogenic factors and endometriosis showed TGF Beta-1 levels and its expressions tend to increase with the stage of endometriosis [10]. Likewise, with Intermediate studies which concluded a relationship and the fact that endoglin plays a role in the pathogenesis of endometriosis, serum endoglin levels can represent endogenous peritoneal fluid and endoglin tissue expression to predicting the endometriosis stage [8].

The previous studies that evaluated the endoglin activity using the immunohistochemical technique. This technique in endometriosis and eutopic endometrium lesions found endoglin expressed in both types of tissue [11,12]. Other studies on peritoneal fluid also found during the angiogenesis, several markers were found associated with inflammatory and angiogenesis including interleukin-6, –β transforming (TGF-β), tumor necrosis factor-α), macrophage migration inhibitory factor (MIF), matrix metalloproteinases (MMP), and vascular endothelial growth factor (VEGF) [13-16]. Based on the angiogenesis in endometriosis, it might suggest that the development of endometriosis is similar to cancer development. Clear cell type ovarian cancer is linked and is thought to originate from endometriosis [16,17]. Angiogenesis in endometriosis might be as the further studies as targeting therapy for endometriosis [18-20].

Angiogenesis in endometriosis is also used as a basis for predicting or screening method for this disease and at the same time might be used to predict the stage of endometriosis. Efforts to determine the angiogenesis process are carried out by examining the angiogenesis marker in the blood serum. Several studies have found a significant increase in levels of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) in endometriosis compared with non-endometriosis [14,15,21,22].

TGF-β signals in endothelial cells could stimulated various processes including proliferation, migration, and adhesion [23]. Endogline is an active signal of endothelium and its expressed during vascular proliferation [24,25]. Signal stimulation caused by involvement of CD105 endoglin in endothelial cells mediated by ALK-1 through this complex pathway whereas TGF-β/ALK5-Smad-3 protein pathway complexes inhibit this stimulation [26].

Endoglin serum is one of the markers used to evaluate several diseases associated with angiogenesis especially in cancer [27,28]. Serum endoglin is also used as a marker in obstetric cases especially preeclampsia. Preeclampsia is a process associated with angiogenesis [29-31]. Serum endoglin has never been used for markers in cases of endometriosis although immunohistochemical examination of endometriotic lesions shows endoglin expression [11,12,32]. Thus, endoglin serum is a potential marker for endometriosis in for screening between endometriosis or not endometriosis even if it is possible to predict the endometrial stages.

Endothelial cells are stable and have a very low turn-over rate, with a doubling time of more than 1000 days whereas in the angiogenic endothelium have a rapid onset called active endothelium [27]. One of the potent markers of the active endothelium is endoglin. In some malignancies, endoglin is found in peritumoral and intratumoral vessels. In addition, many studies have shown that endoglin expression as a better prognostic marker compared with other vascular markers, such as CD31 and von Willebrand factors [28,33]. In all the malignancies studied, endoglin expression determined by immunohistochemical staining is consistently associated with lower patient survival rates. This is not surprising because an increase in vascular tumors is a poor prognosis marker. In addition, in the intestine, breast, prostate, and head and neck malignancy, endoglin is associated with the presence of distant metastatic disease [34].

In conclusion, endoglin levels of menstrual blood in endometriosis patients were compared with without endometriosis. Menstrual blood endogline levels are positively correlated with endometriosis stage.

References

1. Baldi A, Campioni M, Signorile PG. Endometriosis: pathogenesis, diagnosis, therapy and association with cancer (review). Oncol Rep. 2008; 19: 843-846.
2. Annas JY. Perbandingan Ekspresi Prostaglandin E2 (PGE2), Matrix Metalloproteinase 9 (MMP-9) dan Luas implan lesi Endometriosis akibat pemberian Kurkumin dosis 240 mg/Kg BB, 500 mg/KgBB dan 1000/Kg BB pada mencit model Endometriosis. Program PPDS-2, Laporan Penelitian, UNAIR. 2013.
3. Situmorang H, Mutia K. Endometriosis. In Best Practice on IMPERIAL. Hestiantoro A, Natadisastra MR, Sumapraja K, et al. (eds.). 1th ed. Jakarta: CV Sagung Seto. 2012.
4. Jacoeb TZ, Hadisaputra W. Penanganan Endometriosis Panduan Klinis dan Algoritme. Jakarta. CV Sagung Seto. 2009.
5. Elliott JE, Abduljabar H, Morris M. Presurgical management of dysmenorrhea and endometriosis in a patient with Mayer-Rokitansky-Kuster-Hauser syndrome. Fertil Steril. 2011; 96: e86-e89.
6. Trovó de Marqui AB. Genetic polymorphisms and endometriosis: contribution of genes that regulate vascular function and tissue remodeling. Rev Assoc Med Bras (1992). 2012; 58: 620-632.
7. Manuaba IBGF. Kontribusi endoglin pada endometriosis: Analisis terhadap kadar endoglin dan polimorfisme gen

endoglin. Universitas Hasanuddin. Makassar. Indonesia. 2012.
8. Madya F. Hubungan kadar endoglin (CD105) serum dan cairan peritoneum dengan derajat endometriosis. Universitas Hasanuddin. Makassar. Indonesia. 2013.
9. Reis FM, Nascimento LL, Tsigkou A, et al. Activin A and follistatin in menstrual blood: low concentrations in women with dysfunctional uterine bleeding. Reprod Sci. 2007; 14: 383-389.
10. Mappaware NA. Patogenesis Endometriosis; Peran Transforming Growth Factor Beta-1(TGF-β1) pada endometriosis. Universitas Hasanuddin. Makassar. Indonesia. 2013.
11. Hayrabedyan S, Kyurkchiev S, Kehayov I. Endoglin (cd105) and S100A13 as markers of active angiogenesis in endometriosis. Reprod Biol. 2005; 5: 51-67.
12. Kim SH, Choi YM, Chae HD, et al. Increased expression of endoglin in the eutopic en¬dometrium of women with endometriosis. Fertil Steril. 2001; 76: 918-922.
13. Gupta S, Agarwal A, Sekhon L, et al. Serum and peritoneal abnormalities in endometrio¬sis: potential use as diagnostic markers. Minerva Ginecol. 2006; 58: 527-551.
14. Bedaiwy MA, Falcone T. Laboratory testing for endome¬triosis. Clin Chim Acta. 2004; 340: 41-56.
15. Taylor RN, Lebovic DI, Mueller MD. Angiogenic factors in endometriosis. Ann N Y Acad Sci. 2002; 955: 89-100.
16. Kadija S, Stefanovic A, Jeremic K, et al. The utility of hu¬man epididymal protein 4, cancer antigen 125, and risk for malignancy algorithm in ovarian cancer and endometriosis. Int J Gynecol Cancer. 2012; 22: 238-244.
17. Varma R, Rollason T, Gupta JK, et al. Endometriosis and the neoplastic process. Reproduction. 2004; 127: 293-304.
18. Taylor RN, Yu J, Torres PB, et al. Mechanistic and thera¬peutic implications of angiogenesis in endometriosis. Re¬prod Sci. 2009; 16: 140-146.
19. Hull ML, Charnock-Jones DS, Chan CL, et al. Antiangiogenic Agents Are Effective Inhibitors of Endometriosis. J Clin Endocrinol Metab. 2003; 88: 2889-2899.
20. Nap AW, Griffioen AW, Dunselman GA, et al. Antian¬giogenesis therapy for endometriosis. J Clin Endocrinol Metab. 2004; 89: 1089-1095.
21. Abdullah N. Endoglin concentration in peritoneal fluid of patients with endometriosis. Med J Indones. 2013; 22: 88-91.
22. Gagné D, Pagé M, Robitaille G, et al. Levels of vascular endothelial growth factor (VEGF) in serum of patients with endometriosis. Hum Reprod. 2003; 18: 1674-1680.
23. Rius C, Smith JD, Almendro N, et al. Cloning of the promoter region of human endoglin, the target gene for hereditary hemorrhagic telangiectasia type 1. Blood. 1998; 92: 4677-4690.
24. Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily. J Biol Chem. 1999; 274: 584-594.
25. Li C, Hampson IN, Hampson L, et al. CD105 antagonizes the inhibitory signaling of transforming growth factor β1 on human vascular endothelial cells. FASEB J. 2000; 14: 55-64.
26. Bertolino P, Deckers M, Lebrin F, et al. Transforming growth factor-beta signal transduction in angiogenesis and vascular disorders. Chest. 2005; 128: 585S-590S.
27. Duff SE, Li C, Garland JM, et al. CD105 is important for angiogenesis: evidence and potential applications. FASEB J. 2003; 17: 984-992.
28. Fonsatti E, Altomonte M, Nicotra MR, et al. Endoglin (CD105): a powerful therapeutic target on tumor-associated angiogenetic blood vessels. Oncogene. 2003; 22: 6557-6563.
29. Carmeliet P. Angiogenesis in health and disease. Nat Med. 2003; 9: 653-660.
30. Felmeden DC, Blann AD, Lip GY. Angiogenesis: basic pathophysiology and implications for disease. Eur Heart J. 2003; 24: 586-603.
31. Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factor in preeclampsia. N Engl J Med. 2006; 355: 992-1005.
32. Fujishita A, Hasuo A, Khan KN, et al. Immunohistochemical study of angiogenic factors in endometrium and endometriosis. Gynecol Obstet Invest. 1999; 48: 36-44.
33. Maio M, Altomonte M, Fonsatti E. Is it the primetime for endoglin (CD105) in the clinical setting? Cardiovasc Res. 2006; 69: 781-783.
34. Ding S, Li C, Lin S, et al. Comparative Evalution of microvessel density determineted by CD34 or CD 105 in benign and malignant gastric lesions. Hum Pathol. 2006; 37: 861-866.