



Expression Analysis of IL-6 Levels in Cases of Endometriosis Compared To Controls and its Correlation With Different Stage of Disease

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ABSTRACT

Objective: To understand the role of inflammation in endometriosis by analyzing the expression of IL-6 in cases of endometriosis and its co-relation with different stage of disease.

Materials and methods: 168 patients of chronic pelvic pain and or infertility were studied from july 2013-july 2015 in the Department of Obstetrics and Gynaecology, Immunopathology and Molecular and human genetics Dept, Institute of Medical Sciences, Banaras Hindu University, Varanasi . Patients were investigated for routine , infertility work up along with lapro hysterectomy or laparotomy. Peripheral blood sample was taken to estimate for serum IL-6 level in immunology lab of immunopathology department, IMS, BHU. **Results:** Median IL-6 levels were very much elevated in all stages of endometriosis with compared to controls, severe type endometriosis had highest median IL-6 level. **Conclusion:** In our study we have found that IL-6, an inflammatory cytokine increased in ascending order with stage of the disease from minimum to severity.

KEYWORDS : Endometriosis, IL-6.

Introduction: Endometriosis is an estrogen-dependent chronic gynecological disorder and usually found in reproductive-aged women and is associated with pelvic pain and infertility. Its Prevalence is 6–10% in the general population and 35–50% in patients with pelvic pain and/or infertility. IL-6 is an inflammatory marker and is increased with inflammation.

MATERIALS AND METHODS

168 patients of chronic pelvic pain and or infertility were studied from july 2013-july 2015 in the Department of OBGY, Immunopathology Dept, IMS, BHU, Varanasi.

Patients were investigated for routine , infertility work up along with laprohysterectomy or laparotomy. Peripheral blood sample taken to estimate serum IL-6 level in Pathology department, IMS, BHU. **ELISA** technique was used to detect IL-6 level in peripheral blood sample.

OBSERVATION AND RESULTS

Majority of our patients were of the age group of 25-40 years (50%), followed by >40 years of age 42% and only (8%) 25 years age group. However mean age group in severe endometriosis is **31.00±10.311**. The average **age of attaining menarche** was **12.00±0.670** (cases), **12.70±0.544** (controls) **11.33± 0.57** (severe endometriosis). **BMI** has no stastical significance in our study in minimal, mild, and moderate endometriosis but BMI ,much lower in severe endometriosis (**21.4214±2.49140**), when it was classified according to stages of the disease. Even patients of overweight and obesity were also associated with endometriosis may be due to genetic aspect of P53 downregulation or prolonged bleeding due to anovulation. On correlating **socio-economic classes** of all cases, present study had maximum patients in **Kuppuswamy class 3, i.e., lower middle class (34%) and class 2, upper middle class (32%) and 20% in upper lower class**. We found positive correlation between socio-economic status and risk of endometriosis.

Dysmenorrhoea was chief complaint (88%) in all the patient, followed by chronic pelvic pain (84%) and menstrual cycle abnormalities (80%). Regarding menstrual cycle features, we found menorrhagia in upto 51.98% of patients, polymenorrhoea in 24% and hypomenorrhoea in 4% of patients none with oligomenorrhoea, and 20% of pa-

tients had normal menstrual cycles. Menorrhagia followed by polymenorrhoea is found to be the risk factor in cases of endometriosis and adenomyosis in our study. On co-relating the **physical findings** in per vaginum examination **bulky and tender uterus** was found in 30 cases each (**60%**). RV fixed uterus and adnexal mass was found in 20 cases each (40%), thickening/nodularity in POD was found in 4% of cases. However, 4 (**8%**) patients had **normal findings** in examination.

Around 41% of cases were missed in USG and most of the diagnosed cases were adnexal/ovarian endometriosis. Majority of the cases involved ovary (54%) followed by cul de sac (34%) and posterior uterine surface (28%); while only few cases had bowel (8%) and bladder (2%) implant. Adenomyosis was present in about 46% of cases.

Mean IL-6 levels were very much elevated in all types with compared to controls, severe type endometriosis had highest mean IL-6 level.

Table 1 : Level of IL-6 in case and control

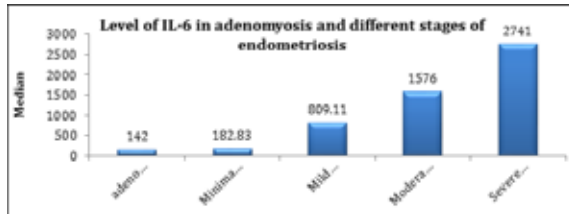
	IL-6 [Median (IQR)]	Mann-Whitney U test (p-value)
Case	535.99 (140.70-1704.0)	0.001
Control	4.43 (2.83-6.11)	



Table 2 : Level of IL-6 in adenomyosis and different stages of endometriosis

Type	IL-6 [Median (IQR)]	Kruskal-Wallis test (p-value)
Adenomyosis (n=30)	142 (33.98-297.98)	<0.001
Minimal (n=18)	182.83 (136.49-229.17)	
Mild (n=24)	809.11 (605.50-1009.0)	
Moderate (n=30)	1576.0 (807.36-1938.0)	
Severe (n=66)	2741.0 (1462.0-3967.0)	

Level of IL-6 in adenomyosis and stages of endometriosis.



DISCUSSION

Cytokines are diverse proteins that play a central role in regulating cell proliferation, activation, motility, adhesion chemotaxis and morphogenesis. **IL-6** is a pleiotropic cytokine that is produced by a variety of cell types, and appears to mediate numerous physiological and pathogenic processes. It is one of the key mediator in the cytokine cascade in the endometriosis and has been shown to be elevated systemically and located to correlate with the disease activity. **Serum levels IL-6** were significantly higher (p value <0.001) in endometriosis group **535.99 (140.70-1704.0)** as compared to control **4.43 (2.83-6.11)** (our Pathology Dept 2015). The mean value in severe disease was comparatively higher as compared to milder forms of the disease. **IL-6** is increased and among correlation, it was increased from adenomyosis to minimal, mild, moderate and severe endometriosis. Patients with adenomyosis has increased IL-6 in comparison to control but less than external endometriosis. Even minimal endometriosis has got significantly increased value **182.83 (136.49-229.17)** in comparison to adenomyosis **142 (33.98-297.98)**. As the disease severity is increasing IL-6 is also increasing. Our study is found similar to study by MA Bedaiwy et al, 2002 and Ehsan EL, Din R et al 2007 where they had found statistically significant difference in serum IL-6 in patients with endometriosis as compared to controls and in contrast to Somigliana et al (2004) who found no statistically significant difference in serum IL-6 concentration between cases of endometriosis and controls. **“Thus IL-6 provides a promising serum marker especially for the non-surgical prediction of endometriosis”**. Our study is found similar to study by Pellicer et al., 1992 and Iwaba et al., 1997 where the median value of **IL-6 increased with the severity** of endometriosis

Characteristics of included studies

Endometriosis in age group	Study
15-40 years	Houston et al(1987)
25-29 years	Kuhong et al(2002)
25-29 years	Missomer SA et al(2004)
No correlation	Vigano P et al(2004)
25-40 years	Our study (2015)
Average age at menarchy in majority of cases	
12.3 years	Liang CC et al(1995)
Early age of menarchy	Cramer D W et al (2002)
Early age of menarchy	Tresolar SA et al(2010)
12.00±0.670	Our study
Socioeconomic status in cases	
Positive correlation	Scott R.B. et al.,1950
Positive correlation	Makhlout Obermeyer et al., 1986, Darows et al., 1993
No association	MP Vessey et al.,1993 & EJ Thomas et al., 1992
Positive correlation	Meigs et al., 1996
Positive correlation	Our study

Risk factor for endometriosis	
Polymenorrhoea, menorrhagia	Darrow SL et al in 1993
Polymenorrhoea, menorrhagia	Vercellini S et al 1997
Menorrhagia, polymenorrhoea	Our study
Common complaint	
Dysmenorrhoea, dyspareunia, chronic pelvic pain	Idhalis Flores et al.,2008
Pelvic pain, dyspareunia	Emmanuel Kalu et al.,2008, Luscombe et al., 2009
Dysmenorrhoea	Our study
Correlation of IL-6 with different stages	Studies
No significant correlation	Hodge et al 1982
Increased with severity	Pellicer et al.,1992
No significant correlation	Bedaiway et al.,1993
Increased with severity	Iwaba et al.,1997
Increased with severity	Our study

CONCLUSION

In our study we have found that **IL-6, an inflammatory cytokine** was increased in ascending order with stage of the disease from minimum to severity. **So, the outcome of our study is that endometriosis is a disease of inflammation and as the inflammation increases, disease progresses.**

In future, if we can prevent the endometriosis progression, by reducing the inflammation.

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