Cytokeratin-19 and Tumor Markers, Biological

Background: This study evaluated the performance of serum CYFRA 21-1 and placental growth factor (PIGF) as screening markers for endometriosis.

Material/Methods: In this prospective study included 81 female patients who underwent laparoscopy to treat benign ovarian tumors. Serum samples were obtained from all study patients before surgery. Serum marker levels, including CYFRA 21-1, PIGF, cancer antigen (CA)125, CA19-9, and human epididymis protein 4 (HE4) were measured using a fluorescence immunoassay technique.

Results: Forty of the patients were diagnosed with endometriosis (the study group) and 41 women were diagnosed with other benign ovarian tumors (the control group). Mean serum CYFRA 21-1 and PIGF levels were not different between these 2 groups (P=0.179 and P=0.865, respectively). Elevated serum CA125 levels (>35 U/mL) and lower CYFRA 21-1 levels (≤2.29 ng/mL) were more frequently observed in the endometriosis study group than in the control group (P<0.0001, and P=0.48, respectively). High serum PIGF levels (>14.2 pg/mL) were observed in both groups (P=0.226). Mean serum CA19-9 levels and HE4 levels, as well as the ROMA (risk of ovarian malignancy Algorithm) score were similar between the 2 groups. Sensitivity (95.0%) and negative predictive value (NPV) (80.0%) of CYFRA 21-1 for diagnosing endometriosis were higher than those of CA125 (sensitivity 67.5%, NPV 74.5%) and PIGF (sensitivity 20.0%, NPV 53.6%). However, the specificity (PIGF 90.2%, CA125 92.7%) and positive predictive value (PPV) (PIGF 66.7%, CA125 87.1%) of PIGF and CA125 for diagnosing endometriosis were higher than those of CYFRA 21-1 (specificity 19.5%, PPV 53.5%).

Conclusions: CYFRA 21-1 and PIGF may be promising markers to identify patients with and without ovarian endometriosis.

MeSH Keywords: Endometriosis • Keratin-19 • Tumor Markers, Biological

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/912787
Background

Endometriosis is a gynecological disease defined by the presence of endometrial-like glands and stroma outside the uterus, including in the pelvic peritoneum, bowel, bladder, uterosacral ligaments, and ovaries.

Symptoms of endometriosis vary widely. However, women with endometriosis commonly experience some kind of pain, such as dysmenorrhea, dyspareunia, and abdominal bloating. Approximately 10% of women of reproductive age suffer from this disease; of those, 30–50% are also infertile and 70% also suffer from pelvic pain [1,2].

At present, the gold standard for diagnosing endometriosis is laparoscopic surgery with histological confirmation. However, diagnostic laparoscopy is an expensive procedure with potential risks for patients. Although other non-invasive diagnostic tools, including ultrasound, pelvic magnetic resonance imaging, markers in peripheral blood or urine, and endometrial biopsies have been investigated, diagnostic laparoscopy remains the preferred option [3,4].

According to a cross-sectional study in Austria and Germany, the median diagnostic delay of endometriosis from the onset of symptoms is 10.4 years (SD: 7.9 years), and 74% of patients experienced at least one false diagnosis [5]. Women with endometriosis suffer from a range of pain, from mild to severe and their quality of life can be significantly threatened. Thus, identifying fast, simple, and non-invasive biomarkers for an early diagnosis of endometriosis is needed. Early identification of biomarkers for endometriosis would shorten the interval between onset of symptoms and diagnosis and improve quality of life for patients who suffer from chronic pelvic pain or infertility.

Some studies have reported that serum or urine CYFRA 21-1 (cytokeratin-19 fragment) levels and serum placental growth factor (PIGF) levels might be useful for an early diagnosis of endometriosis [6–8]. In this prospective study, we estimated the diagnostic performance of serum CYFRA 21-1 and PIGF for endometriosis through comparison with traditional biomarkers for endometriosis and ovarian cancer, cancer antigen (CA)125, CA19-9, and human epididymis protein 4 (HE4), and the risk of ovarian malignancy algorithm (ROMA).

Material and Methods

Patients and sample collection

This was a prospective study conducted at Hallym University Dongtan Sacred Heart Hospital, Korea. Eighty-one female patients who were planning to undergo laparoscopy for the treatment of benign ovarian tumors, which had been diagnosed by ultrasonography, were enrolled in this prospective study between May 2016 and May 2017. Prior to laparoscopy, all patients underwent pelvic ultrasonography to evaluate ovarian tumor characteristics, including the largest diameter, location, and torsion. Exclusion criteria were: 1) active cancer in other sites than the ovary, requiring surgical or medical treatments; 2) known preoperative relapse of a previous cancer; pathologically-confirmed borderlineline or invasive ovarian malignancy during this study. During the laparoscopy, ovarian tumors were removed and examined by a pathologist who specialized in gynecology. Forty patients were diagnosed with endometriosis and 41 patients were diagnosed with other benign tumors. Sixty-four patients underwent unilateral or bilateral ovarian cystectomy and 16 patients underwent unilateral or bilateral oophorectomy.

Blood samples were obtained from all study participants and were collected in sterile tubes containing EDTA at least 2 weeks prior to surgery. The blood samples were centrifuged at 1500g for 10 minutes at 4°C, and the plasma was stored at -20°C until used for measurements. CA125, HE4, and CYFRA 21-1 were determined using an electrochemiluminescence immunoenzymometric assay (Roche Diagnostics, Mannheim, Germany) on the Elecsys system. Serum CA125 and HE4 levels were determined using fully automated chemiluminescence microparticle immunoassays on the Architect i2000 system (Abbott Diagnostics Division, Mannheim, Germany). The ROMA score was calculated using the algorithms proposed by Moore et al. [9]. PIGF was quantified by the Alere PIGF test using the Triage® MeterPro instrument (Alere Srl, Rome, Italy), according to the manufacturer’s instructions. This test is based on a fluorescence immunoassay technique and provides a PIGF measurable range of 12 pg/mL to 3000 pg/mL.

Statistical analysis and sample size

Clinical data registered in an online datasheet were used for statistical analyses. Categorical variables were compared by Fisher’s exact test or the chi-square test, as appropriate. Continuous variables were compared by the t-test. The diagnostic accuracy of the serum markers for discriminating endometriosis from other benign ovarian tumors was evaluated using a receiver operating characteristics (ROC) curve analysis. CYFRA 21-1 and PIGF cutoff values for discriminating endometriosis were determined by the ROC curve analysis. P-values <0.05 were considered significant for all statistical tests. Statistical analyses were performed using SPSS for Windows (version 21.0; SPSS Inc., Chicago, IL, USA) and Medcalc software (version 15.2.2; Medcalc, Ostend, Belgium). Sample size was calculated according to the literature, considering a prevalence of endometriosis of 55±5%, and a specificity and sensitivity of 97±3%. The analysis yielded a minimum of 74 cases [10].
Table 1. Clinical characteristics and preoperative tumor markers in women with endometriosis and the control group.

|                      | Endometriosis (N=40) | Controls (N=41) | P value |
|----------------------|-----------------------|-----------------|---------|
| Age (yrs)            | 35.5±7.93             | 33.7±11.12      | 0.399   |
| Parity               | 0.8±0.88              | 0.98±1.04       | 0.415   |
| Menopause            | 0 (0.0)               | 2 (4.9)         | 0.253   |
| BMI (kg/m²)          | 22.9±3.69             | 23.8±4.05       | 0.284   |
| Tumor characteristics |                      |                 |         |
| Largest diameter (cm)| 6.3±2.91              | 6.3±2.51        | 0.974   |
| Torsion              | 1 (2.5)               | 2 (4.9)         | 0.509   |
| Bilateral tumor      | 11 (27.5)             | 5 (12.2)        | 0.073   |
| Tumor markers        |                       |                 |         |
| CA125 (U/mL)         | 92.6±92.36            | 26.8±36.16      | <0.0001* |
| CA19-9 (U/mL)        | 42.0±50.07            | 25.3±32.26      | 0.093   |
| HE4 (pmol/L)         | 43.5±8.00             | 56.9±71.54      | 0.246   |
| ROMA                 | 6.3±2.63              | 9.2±15.11       | 0.246   |
| CYFRA 21-1 (ng/mL)   | 0.6±0.87              | 0.9±1.35        | 0.179   |
| PIGF (pg/mL)         | 11.3±4.03             | 11.1±4.53       | 0.865   |
| AFS score            |                      |                 |         |
| Stage I (1–5)        | 1                     |                 |         |
| Stage II (6–15)      | 0                     |                 |         |
| Stage III (16–40)    | 12                    |                 |         |
| Stage IV (>40)       | 27                    |                 |         |

Ethics statement

This study was approved by the Institutional Review Board of the Hallym University Dongtan Sacred Heart Hospital (approval No. HDT 2017-03-235-001), and all patients gave informed consent for participation.

Results

Among the 81 female patients, 40 patients were diagnosed with endometriosis by histological confirmation during laparoscopy (endometriosis group). The remaining 41 patients (control group) were diagnosed with mature teratoma (n=33), mucinous cystadenoma (n=5), serous cystadenoma (n=2), or a functional cyst (n=1). There was no case of coexistence of 2 or 3 pathologies in ovarian tumors. The mean age was 34.5 years. Almost all patients were premenopausal, except for 2 postmenopausal patients in the control group.

The patient characteristics, including age, parity, and body mass index were not different between the 2 groups (Table 1). Tumor characteristics, such as the largest diameter, torsion, and bilaterality, were similar between the 2 groups (Table 1).

Among the 40 patients in the endometriosis group, 39 patients had stage III or IV disease (Table 1).

Serum markers, including CA125, CA19-9, HE4, ROMA, CYFRA 21-1, and PIGF were compared between the 2 groups (Table 1). Mean serum CA125 level was significantly higher in the endometriosis group than in the control group (P<0.0001). However, mean serum CYFRA 21-1 and PIGF levels were not different between the 2 groups (P=0.179 and P=0.865). In addition, mean serum CA19-9 and HE4 levels, as well as the ROMA score were similar between the 2 groups.

The correlations between endometriosis and the serum markers are described in Table 2. Elevated serum CA 125 levels (>35 U/mL) and lower CYFRA 21-1 levels (<2.29 ng/mL) were more frequently observed in the endometriosis group than in the control group (P<0.0001). However, mean serum CYFRA 21-1 and PIGF levels were not different between the 2 groups (P=0.179 and P=0.865). In contrast, elevated serum PIGF levels (>14.2 pg/mL) were similarly observed in both groups (P=0.226).

The diagnostic accuracy of serum CYFRA 21-1, PIGF, and CA125 for endometriosis is shown in Table 3. The sensitivity (95.0%) and negative predictive value (NPV) (80.0%) of CYFRA 21-1 for diagnosing endometriosis were higher than the values for
CA125 (sensitivity 67.5%, NPV 74.0%) and PIGF (sensitivity 20.0%, NPV 53.6%). However, the specificity and positive predictive value (PPV) of PIGF and CA125 for diagnosing endometriosis were higher than those of CYFRA 21-1 (specificity was PIGF 90.2%, CA125 90.2%, CYFRA 21-1 9.5% and PPV was PIGF 66.7%, CA125 87.1%, CYFRA 21-1 53.5%). The combination of CYFRA 21-1 and CA125 for diagnosing endometriosis showed similar sensitivity (62.5%) and better specificity (92.7%), NPV (80.5%), and PPV (89.3%) in comparison to CA125 only.

**Table 2.** Correlation between endometriosis and serum levels of tumor markers.

| Marker   | Endometriosis (N=40) | Controls (N=41) | P value |
|----------|----------------------|-----------------|---------|
| CA125    |                      |                 |         |
| Elevated (>35 U/mL) | 27 (67.5) | 4 (9.8) | <0.0001* |
| Non-elevated | 13 (32.5) | 37 (90.2) |         |
| CA19-9   |                      |                 | 0.534   |
| Elevated (>27 U/mL) | 12 (30.0) | 13 (31.7) |         |
| Non-elevated | 28 (70.0) | 28 (68.3) |         |
| HE4      |                      |                 | 0.264   |
| Elevated (>60 pmol/L) | 2 (5.0) | 6 (14.6) |         |
| Non-elevated | 38 (95.0) | 35 (85.4) |         |
| CYFRA 21-1 |                      |                 | 0.048*  |
| Elevated (>2.29 ng/mL) | 2 (5.0) | 8 (19.5) |         |
| Non-elevated | 38 (95.0) | 33 (80.5) |         |
| PIGF     |                      |                 | 0.226   |
| Elevated (>14.2 pg/mL) | 8 (20.0) | 4 (9.8) |         |
| Non-elevated | 32 (80.0) | 37 (90.2) |         |

**Table 3.** Diagnostic accuracy of tumor markers for discriminating endometriosis from other benign tumors.

| Marker         | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|----------------|-----------------|-----------------|-------------------------------|-------------------------------|
| CYFRA 21-1     | 38/40 (95.0)    | 8/41 (19.5)     | 38/71 (53.5)                 | 8/10 (80.0)                  |
| PIGF           | 8/40 (20.0)     | 37/41 (90.2)    | 8/12 (66.7)                  | 37/69 (53.6)                |
| CA125          | 27/40 (67.5)    | 37/41 (90.2)    | 27/31 (87.1)                 | 37/50 (74.0)                |
| CYFRA 21-1 & CA125 | 25/40 (62.5) | 38/41 (92.7)   | 25/28 (89.3)                 | 38/53 (74.5)                |

**Discussion**

To date, the gold standard for diagnosing endometriosis is direct visualization of lesions during laparoscopic surgery [11]. Although this surgical diagnosis is relatively accurate and operator-independent, there can also be risks inherent to the procedure, such as adjacent organ damage, infection, and adhesion formation [12]. In addition, complications associated with general anesthesia as well as the high cost of surgery should not be ignored [12].

A simple and non-invasive diagnostic tool is required to minimize unnecessary invasive procedures. A number of studies have attempted to identify peripheral blood or urine markers capable of diagnosing or excluding endometriosis [13–15]. Endometriosis is well-known to be hormone-dependent and correlated with inflammation. Therefore, most of the putative endometriosis markers are glycoproteins, hormones, growth or adhesion factors, or proteins that are associated with immunology or angiogenesis [12,13,15,16]. The most well-known and widely used blood marker is CA125 [15,17]. Several studies have reported that serum CA125 level is a useful marker for diagnosing endometriosis, as it is significantly correlated with disease severity, especially in ovarian endometrioma [15,18,19]. However, CA125 is not specific to endometriosis and can also be increased in patients with ovarian cancer and other benign conditions such as uterine fibroids, adenomyosis, and...
pelvic inflammatory disease [20,21]. Moreover, the sensitivity of CA125 for detecting early-stage endometriosis appears to be low [22]. A meta-analysis that assessed the diagnostic performance of serum CA125 levels for detecting endometriosis revealed that the sensitivity for stage I–IV endometriosis was 50% and specificity was 72%, and sensitivity and specificity in stage III–IV endometriosis were 60% and 80%, respectively [22].

Although many studies have tried to detect useful markers for early diagnosis of endometriosis, a novel biomarker that shows high sensitivity and specificity remains to be identified [7,12,15,17,23].

Several studies have reported that serum or urine CYFRA 21-1 and serum PIGF might be valuable markers for diagnosing endometriosis [7,8,24].

Cytokeratin 19 (CK-19) is a member of the type I cytokeratin protein genes and a cell structural protein coding for intermediate filament acidic proteins [25]. CK-19 is expressed in most epithelial cells and many types of malignancies such as lung and esophageal cancers [26–28]. The function and role of CK-19 in endometriosis have yet to be clarified. CK-19 can be detected in epithelial cells of the endometrium in women with and without endometriosis, as well as in endometriotic lesions [29]. CK-19 can also be detected in menstrual fluid, peritoneal fluid, normal peritoneum, urine, and ectopic endometriotic lesions from women with endometriosis [8,30]. CYFRA 21-1 is a CK-19 fragment that is soluble in serum and may be a useful circulating tumor marker [31]. A recent study using proteomic techniques and mass spectrometry in Australia revealed that urine CYFRA 21-1 was highly upregulated in the urine of women with endometriosis [8]. However, the study could not explain the mechanism of how urine CYFRA 21-1 was upregulated. Another prospective study that evaluated serum and urine CYFRA 21-1 in endometriosis reported no differences in serum or urine CYFRA 21-1 levels between women with and without endometriosis [7]. Similarly, in our results, serum CYFRA 21-1 level was not different between women in the endometriosis group and the control group. A lower CYFRA 21-1 level (≤2.29 ng/mL) was more frequently observed in women with endometriosis than the control. The diagnostic accuracy of serum CYFRA 21-1 for endometriosis was comparable to that of CA125. Specifically, the sensitivity of serum CYFRA 21-1 was significantly higher than that of CA125. In addition, the combination of serum CYFRA 21-1 and CA125 for diagnosing endometriosis showed comparable sensitivity, specificity, NPV, and better PPV to those of CA125.

PIGF, which was originally identified in the placenta, is a member of the proangiogenic vascular endothelial growth factor family and has been proposed to control trophoblast growth, differentiation, and invasion [32–34]. It is well-known that PIGF contributes to angiogenetic switching during pregnancy, wound healing, ischemic conditions, and tumor growth [33–35]. In addition, PIGF may facilitate metastasis by increasing the motility and invasion of malignant cells [7]. Several studies have reported that serum and plasma levels of PIGF are highly correlated with tumor stage and poor survival of patients with various tumors [36–39]. The angiogenetic and prometastatic activities of PIGF suggest that it could be a candidate biomarker for diagnosing endometriosis. A prospective study that measured peritoneal PIGF levels during laparoscopic surgery reported that women with endometriosis show significantly higher peritoneal PIGF levels than those with cystadenoma [40]. This suggested that production of PIGF may contribute to the pathogenesis of endometriosis by promoting neovascularization [40]. A case-control study including 13 women with histologically confirmed endometriosis reported that the median PIGF value was higher in the endometriosis group than in the control group (14.7 pg/mL versus 13.8 pg/mL, P=0.004) [7]. In our results, higher PIGF levels (>14.2 pg/mL) tended to be more frequently observed in the endometriosis group than in the control group (20% versus 9.8%, respectively, P=0.226). We consider that the differences between our results and prior results might stem from differences in patient distribution, study setting, and the small number of study participants. Our control group included women with benign ovarian tumors, which can be associated with an angiogenetic condition and elevated PIGF. In addition, all of our participants were Korean women, which was different from prior studies with only Western women.

In our study, we compared the diagnostic function of serum CYFRA 21-1 and PIGF to that of conventional serum markers for early detection of endometriosis. CYFRA 21-1 showed better sensitivity and NPV than CA125, which is a representative serum marker for detecting endometriosis. Serum PIGF showed comparable specificity to that of CA125.

Our study had some limitations. First, the endometriosis group and control group were relatively small to fully evaluate the diagnostic performance of serum markers. Second, the control group consisted of women with other benign ovarian tumors, which could also be associated with cytokeratin and PIGF expression [7,41,42]. If we used a healthy control group, the differences in the serum markers between the 2 groups may have been more significant. Third, the study group consisted of almost all stage III or IV endometriosis cases, which made it difficult to evaluate the performance of serum markers for detecting early endometriosis.

**Conclusions**

Our study provided valuable information and determined that serum CYFRA 21-1 and PIGF might be promising markers for diagnosing early-stage endometriosis.
endometriosis. A larger-scaled prospective study with healthy controls versus an early-stage endometriosis group will be needed to clarify the diagnostic function of serum CYFRA 21-1 and PIGF.

References:

1. Giudice LC, Kao LC. Endometriosis. Lancet, 2004; 364(9447): 1789–99
2. Bulan SE. Endometriosis. N Engl J Med, 2009; 360(3): 268–79
3. May KE, Villar J, Kirtley S et al: Endometrial alterations in endometriosis: a systematic review of putative biomarkers. Hum Reprod Update, 2011; 17(5): 637–53
4. Sibai BM. Biomarker for hypertension-preclampsia: Are we close yet? Am J Obstet Gynecol, 2007; 197(1): 1–2
5. Hudelst G, Fritzner N, Thomas A et al: Diagnostic delay for endometriosis in Austria and Germany: causes and possible consequences. Hum Reprod, 2012; 27(12): 3412–16
6. Lessey BA, Savaris RF, All S et al: Diagnostic accuracy of urinary cytokeratin 19 fragment for endometriosis. Reproductive sciences. 2015; 22(5): 551–55
7. Zucchin C, De Sanctis P, Facchini C et al: Performance of circulating placental growth factor as a screening marker for diagnosis of ovarian endometriosis: A pilot study. Int J Fertil Steril, 2016; 9(4): 483–89
8. Tokushige N, Marham R, Crossett B et al: Discovery of a novel biomarker in the urine in women with endometriosis. Fertil Steril, 2011; 95(1): 46–49
9. Moore RG, McMeekin DS, Bao AK et al: A novel multiple marker biosay utilizing HE4 and CA15-3 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol, 2009; 112(1): 40–46
10. Malhotra RK, Indrayan A. A simple nomogram for sample size for estimating sensitivity and specificity of medical tests. Indian J Ophthalmol, 2010; 58(6): 519–22
11. Kennedy S, Bergqvist A, Chapron C et al: ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod, 2005; 20(10): 2698–704
12. Fassbender A, Burney RO, O DF et al: Update on biomarkers for the detection of endometriosis. Biomed Res Int, 2015; 2015: 130854
13. Fassbender A, Vodolazaikia A, Saunders P et al: Biomarkers of endometriosis. Fertil Steril, 2013; 99(4): 1135–45
14. D’Sa Hooge TM, Mihaly AM, Simsa P et al: Why we need a noninvasive diagnostic test for minimal to mild endometriosis with a high sensitivity. Gynecol Obstet Invest, 2006; 62(3): 136–38
15. May KE, Conduit-Hulbert SA, Villar J et al: Peripheral biomarkers of endometriosis: A systematic review. Hum Reprod Update, 2010; 16(6): 651–74
16. Othman Eel D, Hornung D, Al-Hendy A: Biomarkers of endometriosis. Expert Opin Med Diagn, 2008; 2(7): 741–52
17. Vodolazaika A, El-Aalam Y, Popov D et al: Evaluation of a panel of 28 biomarkers for the non-invasive diagnosis of endometriosis. Hum Reprod, 2012; 27(9): 2698–711
18. Socolov R, Butereau SA, Angioni S et al: The value of serological markers in the diagnosis and prognosis of endometriosis: A prospective case-control study. Eur J Obstet Gynecol Reprod Biol, 2011; 154(2): 215–17
19. Mabrouk M, Elmakky A, Caramelli E et al: Performance of peripheral (serum and molecular) blood markers for diagnosis of endometriosis. Arch Gynecol Obstet, 2012; 285(5): 1307–12
20. Check JH. CA-125 as a biomarker for malignant transformation of endometriosis. Fertil Steril, 2009; 91(5): e35; author reply e36
21. He RH, Yao WM, Wu LY, Mao Y: Highly elevated serum CA-125 levels in patients with non-malignant gynecological diseases. Arch Gynecol Obstet, 2011; 283(Suppl. 1): 107–10
22. Mol BW, Bayram N, Lijmer JG et al: The performance of CA-125 measurement in the detection of endometriosis: A meta-analysis. Fertil Steril, 1998; 70(6): 1101–08
23. Tuten A, Kucur M, Imamoglu M et al: Copeptin is associated with the severity of endometriosis. Arch Gynecol Obstet, 2014; 290(1): 75–82
24. Kuesel L, Jaeger-Lansky A, Pateský P et al: Cytokeratin-19 as a biomarker in urine and in serum for the diagnosis of endometriosis – a prospective study. Gynecol Endocrinol, 2014; 30(1): 38–41
25. Moll R: [Cytokeratins as markers of differentiation. Expression profiles in epithelia and epithelial tumors]. Veroff Pathol,1993; 142: 1–197 [in German]
26. Kosacka M, Jankowska R: Comparison of cytokeratin 19 expression in tumor tissue and serum CYFRA 21-1 levels in non-small cell lung cancer. Pol Arch Med Wewn, 2009; 119(1–2): 33–37
27. Pujoil IL, Giegerer I, Daures JP et al: Serum fragment of cytokeratin subunit 19 measured by CYFRA 21-1 immunoradiometric assay as a marker of lung cancer. Cancer Res, 1993; 53(1): 61–66
28. Novoa M, Bendit I, Garicocbea B, del Giglio A: Reverse transcriptase-polymerase chain reaction analysis of cytokeratin 19 expression in the peripheral blood mononuclear cells of normal female blood donors. Mol Pathol, 1997; 50(4): 209–11
29. Bartek J, Bartkova J, Taylor-Papadimitraki et al: Differential expression of keratin 19 in normal human epithelial tissues revealed by monospecific monoclonal antibodies. Histochem J, 1986; 18(10): 565–75
30. van der Linden PJ, Dunsulan GA, de Goel AF et al: Epithelial cells in peritoneal fluid – of endometriosis origin? Am J Obstet Gynecol, 1995; 175(2): 566–70
31. Holdenrieder S, Wehnli B, Hettwer K et al: Carcinoembryonic antigen and cytokeratin-19 fragments in vascular endothelial growth factor signaling implicated in neuroprotective effects of placental growth factor in an in vitro ischemic model. Brain Res, 2010; 1357: 1–8
32. Liu H, Hommou O, Harada K et al: Neutrophil protease-8 (NETs) of human mesenchymal stem cells after cerebral ischaemia. Brain, 2006; 129(Pt 10): 2734–45
33. Autiero M, Luttun A, Tjwa M, Carmeliet P: Placental growth factor and its receptor, vascular endothelial growth factor receptor-1: Novel targets for stimulation of ischemic tissue revascularization and inhibition of angiogenic and inflammatory disorders. J Thromb Haemost, 2003; 1(7): 1356–70
34. Chen J, Ye L, Zhang L, Liang WG: Placental growth factor, PLGF, influences the motility of lung cancer cells, the role of Rho associated kinase, Rock1. J Cell Biochem, 2008; 105(1): 313–20
35. Taylor AP, Leon E, Goldberg DM: Placental growth factor (PIGF) enhances breast cancer cell motility by mobilising ERK1/2 phosphorylation and cytoskeletal rearrangement. Br J Cancer, 2010; 103(1): 82–89
36. Li B, Wang C, Zhang Y et al: Elevated PIGF contributes to small-cell lung cancer brain metastasis. Oncogene, 2013; 32(24): 2952–62
37. Cheng SJ, Lee JL, Cheng SL et al: Increased serum placenta growth factor level is significantly associated with progression, recurrence and poor prognosis of oral squamous cell carcinoma. Oral Oncol, 2012; 48(5): 424–28
38. Suzuki M, Sugita-Ogasawara M, Katano K, Suzuki K: Women with endometriosis have increased levels of placental growth factor in the peritoneal fluid compared with women with cystadenomas. Hum Reprod, 2003; 18(12): 2955–98
39. Tsuji K, Wato M, Hayashi T et al: The expression of cytokeratin in keratocystic odontogenic tumor, orthokeratinized odontogenic cyst, dentigerous cyst, radicular cyst and dermoid cyst. Med Mal Morphol, 2014; 47(3): 156–61
40. Carmeliet P, Moons I, Luttun A et al: Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med, 2001; 7(5): 755–83

Conflicts of interest
None.