The Use of Peritoneal and/or Serum Biomarkers as a Non-Invasive Method for Diagnosing Endometriosis

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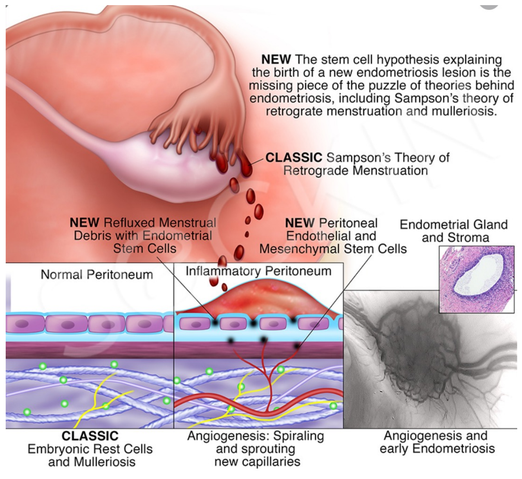
Background

- Endometriosis affects more than four million women of reproductive age in the United States and approximately 200 million women worldwide
- Endometriosis is defined as endometrial glands and stroma that occur outside the uterine cavity. It is a non-malignant condition that is estrogen-dependent & responds to cyclical hormonal changes
- There are three different subcategories of endometriosis: superficial peritoneal lesions, ovarian lesions (endometriomas), and deep infiltrating endometriosis (DIE)
- Risk factors for developing endometriosis include nulliparity, early menarche, late menopause, lower BMI, and obstruction of menstrual flow
- Effects of the condition include chronic pelvic pain, sub-fertility, and urinary and gastrointestinal symptoms

Pathogenesis



- Seckin T., Chu A., Baum S. (2018) Hysteroscopic Findings in the Endometriosis Patient. In: Tinelli A., Alonso Pacheco L., Haimovich S. (eds) Hysteroscopy. Springer, Cham. https://doi.org/10.1007/978-3-319-57559-9_45

Justification & Rationale

- Currently, the only way to definitively diagnose endometriosis is through surgical laparoscopy with histological biopsy
- The average time for an individual to be diagnosed with endometriosis from onset of symptoms to diagnosis is roughly seven years
- There is currently no non-invasive out-patient test that can accurately diagnose endometriosis.
- Laparoscopy with biopsy has risks, such as surgical adhesions, post-operative infection, complications from anesthesia, and injury to surrounding organs and tissues
- Rationale for use of biomarkers: ectopic endometriotic lesions secrete chemokines into their surrounding tissues, recruiting immune cells, which in turn secrete cytokines and growth factors

PICO

In Patients with Clinical Findings Associated with Endometriosis, can Peritoneal and/or Serum Biomarkers be Used in Lieu of Laparoscopy to Produce a Sensitive and Specific Diagnosis of Endometriosis?

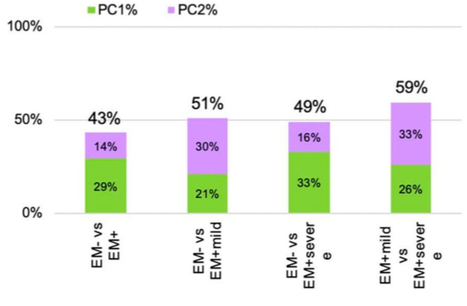
- P: Patients with clinical findings associated with endometriosis
- I: Peritoneal and/or serum biomarkers
- C: Laparoscopy (with or without histological confirmation)
- O: Sensitive and specific diagnosis of endometriosis

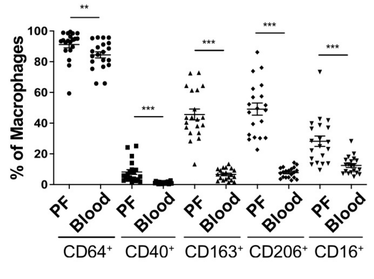
Methods

Gupta et al.	• Systematic review of 54 studies with a total of 2,729 subjects were analyzed (mean of 49 subjects per study); studies included peer-reviewed randomized control trials or cross-sectional studies • All subjects were women of reproductive age with a diagnosis of one or more of the following: ovarian, peritoneal or deep infiltrating endometriosis • Biomarkers analyzed were from eutopic endometrial, serum and menstrual fluid sources
Zhou et al.	• Peritoneal fluid of 73 endometriosis patients were compared to that of 59 non-endometriosis controls • Endometriosis patients were separated into mild or severe and into sub-phenotypes of ovarian, peritoneal and deep infiltrating endometriosis • 48 different cytokines were analyzed using Multiplex immunoassay
Guo et al.	• Peritoneal samples and peripheral blood samples were taken from 27 endometriosis patients and 11 non-endometriosis controls; disease severity was also separated into mild/moderate and moderate/severe • Mass cytometry was performed with a panel of 33 different antibodies to profile the innate and adaptive immune environments

Results

- In 27 out of the 54 studies included in the systematic review, 22 different biomarkers were shown to have significant associations with endometriosis; these included angiogenesis and growth factors, cell adhesion molecules, endometrial and mitochondrial proteome, myogenic markers, neural markers, and tumor marker CA-125.
  - » Neural fiber marker PGP 9.5 and hormonal marker CYP19 being the two most well-studied
- A cytokine signature comprised of IFN-α2, IL-12p70, IL-18, SCGF-β, VEGF-A, IL-3, and HGF that distinguished endometriosis patients from non-endometriosis patients in the Zhou et al study
- More significant difference in immune profiles were seen in mild/moderate endometriosis than with moderate/severe endometriosis
- The Gou et al study showed that most cells found in peritoneal and peripheral blood samples of endometriosis patients were immune cells, and there was a greater overall number of immune cells and variation in peritoneal fluid compared to peripheral blood samples in endometriosis patients





- Results from the Zhou et al. study on the left - differentiating cytokine profiles with sub phenotypes of endometriosis
  - » Total scores at top of bars represent total principal component score, and therefore ability to distinguish between conditions
- Results from the Gou et al. study on the right - proportion of macrophages in peritoneal fluid vs. peripheral blood samples

EM- = non-endometriosis patients, EM+ = endometriosis patients (mild vs severe), PF= peritoneal fluid

Study Limitations

- Menstrual cycle phase and hormone therapy were not well controlled in any of the studies
- In the Guo study, all participants were recruited from the same health center in the UK
- The Zhou study included participants from only two hospitals, both in Singapore

Conclusions & Future Directions

- Not enough evidence yet to replace laparoscopy with peritoneal or serum biomarkers as a method of diagnosis of endometriosis
- Overall, peritoneal biomarkers may be more specific for endometriosis than serum biomarkers
- More studies should be done with more diverse and larger sample sizes from multiple healthcare institutions
- Future studies should include controls for menstrual phase and hormone therapy
- It would be interesting to have future studies assess the sensitivity and specificity of using biomarkers plus physical exam findings and/or other noninvasive tests such as trans-vaginal ultrasound to diagnose endometriosis compared to laparoscopy

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References

- Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. Am J Obstet Gynecol 2019;**220**(4):354 e1-54 e12 doi: 10.1016/j.ajog.2018.12.039[published Online First: Epub Date]|.
- Schenken RS BR, Eckler K. Endometriosis: Pathogenesis, clinical features, and diagnosis. In: Post TW e, ed. Waltham, MA: UpToDate Inc., 2020.
- Audebert A, Petousis S, Margioula-Siarkou C, Ravanos K, Prapas N, Prapas Y. Anatomic distribution of endometriosis: A reappraisal based on series of 1101 patients. Eur J Obstet Gynecol Reprod Biol 2018;**230**:36-40 doi: 10.1016/j.ejogrb.2018.09.001[published Online First: Epub Date]|.
- Zhou J, Chern BSM, Barton-Smith P, et al. Peritoneal Fluid Cytokines Reveal New Insights of Endometriosis Subphenotypes. Int J Mol Sci 2020;**21**(10) doi: 10.3390/ijms21103515[published Online First: Epub Date]|.
- McKinnon BD, Bertschi D, Bersinger NA, Mueller MD. Inflammation and nerve fiber interaction in endometriotic pain. Trends Endocrinol Metab 2015;**26**(1):1-10 doi: 10.1016/j.tem.2014.10.003[published Online First: Epub Date]|.
- Surrey E, Soliman AM, Trenz H, Blauer-Peterson C, Sluis A. Impact of Endometriosis Diagnostic Delays on Healthcare Resource Utilization and Costs. Adv Ther 2020;**37**(3):1087-99 doi: 10.1007/s12325-019-01215-x[published Online First: Epub Date]|.
- 12. Schenken RS, Barbieri RL, Eckler K. Endometriosis: Treatment of pelvic pain. In: Post TW, ed. Waltham, MA: UpToDate Inc. 2020. Accessed September 8, 2020.
- 13. Woo J SR. In: McPhee SJ RM, ed. Current Medical Diagnosis and Treatment 2020. Papadakis MA: McGraw-Hill.
- Matsuzaki S, Canis M, Pouly JL, Rabischong B, Botchorishvili R, Mage G. Relationship between delay of surgical diagnosis and severity of disease in patients with symptomatic deep infiltrating endometriosis. Fertil Steril 2006;**86**(5):1314-6; discussion 17 doi: 10.1016/j.fertnstert.2006.03.048[published Online First: Epub Date]|.
- Gao X, Yeh YC, Outley J, Simon J, Botteman M, Spalding J. Health-related quality of life burden of women with endometriosis: a literature review. Curr Med Res Opin 2006;**22**(9):1787-97 doi: 10.1185/030079906x121084[published Online First: Epub Date]|.
- Guo M, Baffigil C, Tapmeier T, et al. Mass cytometry analysis reveals a distinct immune environment in peritoneal fluid in endometriosis: a characterisation study. BMC Med 2020;**18**(1):3 doi: 10.1186/s12916-019-1470-y[published Online First: Epub Date]|.
- Gupta D, Hull ML, Fraser I, et al. Endometrial biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database Syst Rev 2016;**4**(4):Cd012165 doi: 10.1002/14651858.Cd012165[published Online First: Epub Date]|.