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O soro de mulheres com endometriose altera os níveis de citocinas produzidas pelas células estromais e endoteliais uterinas cocultivadas em sistema 3D

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RESUMO

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A endometriose é uma doença inflamatória crônica caracterizada pela presença e crescimento de tecido endometrial ectópico. Ela afeta 10% a 15% de mulheres em idade reprodutiva e está associada à inflamação grave e infertilidade. O perfil de fatores imunológicos sistêmicos alterados parece ser o principal fator associado com a infertilidade nesta doença, independentemente da gravidade da lesão associada à endometriose. Neste estudo, através do cocultivo tridimensional (3D) de endométrio parcialmente reconstituído, exploramos a possibilidade de fatores presentes no soro de mulheres com endometriose modificarem o perfil de citocinas produzidas pelo endométrio, determinando alterações que podem afetar a fertilidade. As amostras foram coletadas após obtenção do consentimento informado por escrito das pacientes (Comitê de Ética em Pesquisa em Seres Humanos da USP, nº 692457). As biópsias do endométrio (n = 15) e soro (n = 15) foram coletadas de pacientes sem endometriose da clínica Huntington Medicina Reprodutiva, São Paulo, Brasil. O soro das pacientes com endometriose (que fazem uso de anticoncepcionais, n = 10 e não tratadas, pós-cirurgia, n = 5) foi obtido nessa clínica e no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, SP. As biópsias foram digeridas com colagenase II / DNAase I e filtradas para a retenção das glândulas endometriais. *Beads* magnéticas anti-CD105 (MACS) foram utilizadas para a seleção positiva de células endoteliais e negativa de células estromais. Para construir o ambiente 3D, 0,1 x 10^6 de células estromais em meio DEMEM/F12 foram adicionadas a uma mistura de matriz extracelular (fibronectina e colágeno V, I e III) e colocadas em placas de 48 poços. Após 12 horas, em condições de cultura (37°C, 5% de CO_2), as células endoteliais foram adicionadas ao sistema (0,1 x 10^6 células) e após 24 horas, foi adicionado o soro de mulheres saudáveis ou com endometriose, compondo os seguintes grupos (n = 3-8): i) soro de pacientes saudáveis; ii) soro de pacientes com endometriose; iii) soro de pacientes com endometriose, que fazem uso de anticoncepcionais. O homogenato celular foi coletado após 24 e 48h e o perfil de citocinas avaliado por CBA (*Cytometric Bead Array)*. O endométrio reconstituído foi morfologicamente analisado e caracterizado por imunofluorescência utilizando marcadores específicos para células de origem mesenquimal, células deciduais, endoteliais e epiteliais mostrando uma típica organização endotélio-estroma. Ele também respondeu ao perfil de citocinas presentes no soro, produzindo citocinas que estão envolvidas com a regulação da resposta imune: houve predomínio das citocinas: IL-2, IL-10, IL-6, IFN-γ e TNF-α com uma tendência ao perfil inflamatório. Em relação a este grupo, o uso de soro de pacientes tratadas tendeu a uma não exacerbação do processo inflamatório (IL-4, IL-6 e IL-8). O modelo experimental estudado mostrou-se uma ferramenta elegante que pode nortear inúmeros estudos envolvendo o ambiente uterino, possibilitando futuras estratégias de análise da fisiopatologia endometrial em condições impactantes como aquelas acometidas por doenças, como a endometriose, que levam à infertilidade.

Palavras-chave: Cocultura. Cultura 3D. Endométrio. Endometriose. Citocinas.

ABSTRACT

BORGATO, C.G. **Serum from women with endometriosis altering the levels of cytokines produced by stromal and endothelial endometrial cells in 3D co-culture system.** 2016 119 f. Dissertation (Masther thesis in Cell and Tissue Biology) – Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo, 2016.

Endometriosis is a chronic inflammatory disease characterized by the presence and growth of ectopic endometrial tissue. It affects 10% to 15% of women in reproductive age and is associated with severe inflammation and infertility. The altered profile of systemic immunological factors seems to be linked to infertility in this disease, regardless of the severity of the endometriosis lesions. In this study, through a three-dimensional (3D) co-culture system of a partially reconstituted endometrium, we explored the possibility that factors present in the serum of women with endometriosis affect the profile of cytokines produced by the endometrium, determining changes that can affect fertility. Samples were collected after obtaining written informed consent (the Research Ethics Committee of USP Human Beings, no. 692457). Endometrial biopsies (n = 15) and serum (n = 15) were collected from patients without endometriosis from Huntington Reproductive Medicine Clinical, São Paulo, Brazil. The serum of patients with endometriosis (using contraceptives, n = 10 and untreated, post-surgery n = 5) was obtained from this clinic and Hospital of Medical School of the University of São Paulo, SP. Biopsies were digested with collagenase II / DNAase I and filtered to retention of endometrial glands. Magnetic beads anti-CD105 (MACS) were used for positive and negative selection of endothelial cells and stromal cells, respectively. The cells were resuspended in supplemented medium (DMEM / F12). To construct the 3D environment, 0.1 x 106 stromal cells in the medium were added to a mixture of extracellular matrix components (fibronectin and collagen V, I and III) and plated in 48 well plates. After 12 hours in culture conditions (37°C with 5% CO2), the endothelial cells were added to the system (0.1 x 106 cells) on the surface of the gelled culture. After 24 hours, the medium was either replaced by serum of women with endometriosis or healthy, as follows (n = 3-8): i) serum from healthy women, without endometriosis; ii) serum from patients with endometriosis; iii) serum of patients with endometriosis using contraceptives. The system remained in culture conditions for further 24 and 48 h. The homogenate of the cells was collected to assess the cytokine profile by CBA (Cytometric Bead Array). The reconstituted endometrium was morphologically examined and characterized by immunofluorescence using specific markers for mesenchymal, decidual, endothelial and epithelial cells showing a typical stromal-endothelial organization. It also showed to be able to respond to the cytokines present in sera, producing cytokines involved in the regulation of immune response, with a predominance of IL-2, IL-6, IL-10, IFN-g, and TNF-a, with an inflammatory tendency. In comparison with this group, the group of sera from treated patients showed a cytokine profile, which tended to a non-exacerbating inflammatory profile (IL-4, IL-6, and IL-8). The experimental model, here explained, proved to be an elegant tool that can be used in numerous studies involving the uterine environment, enabling future strategies for analysis of endometrial pathophysiology in impactful conditions like those affected by diseases such as endometriosis, leading to infertility

Keywords: Co-culture. 3D culture. Endometrium. Endometriosis. Cytokines.

INTRODUÇÃO

A infertilidade é atribuída a várias causas, dentre elas diversos fatores relacionados a falhas de implantação e qualidade embrionária (DE ZIEGLER et al., 2016). Apesar dos muitos estudos já descritos na literatura, as causas e alterações que levam a essas falhas ainda não foram totalmente elucidadas. A importância do tecido uterino nesse complexo processo é ímpar. Estudos têm mostrado que a inabilidade uterina em manter um ambiente adequado para o estabelecimento da receptividade endometrial, para a implantação embrionária ou para o desenvolvimento embrionário é uma das causas que prevalece nas perdas embrionárias recorrentes (NORWITZ; SCHUST; FISHER, 2001).

Dentre as patologias que levam a perdas embrionárias recorrentes, destacam-se aquelas sem causa aparente e a endometriose (YOVICH et al., 1988). Particularmente a endometriose, caracterizada pelo crescimento de tecido endometrial fora do útero, é uma doença que afeta milhões de mulheres na fase reprodutiva em todo o mundo (MEULEMAN et al., 2009). Mulheres com endometriose apresentam, entre outros sintomas, dores pélvicas crônicas e subfertilidade (VIGANÒ et al., 2004). A diminuição da fertilidade nesta patologia se deve principalmente à redução da qualidade oocitária e à perda da receptividade endometrial durante a janela de implantação, causadas por alterações do perfil inflamatório destas pacientes tanto na cavidade pélvica quanto no sangue periférico, sugerindo uma possível base imunológica (GIUDICE et al., 2002; GIUDICE; KAO, 2004; LEBOVIC et al., 2001).

Além disso, evidências também apontam para alterações no endométrio eutópico dessas mulheres, no que diz respeito à estrutura, atividade proliferativa, componentes imunológicos e, produção e responsividade a citocinas (MINICI et al., 2008; SHARPE-TIMMS, 2001), sugerindo que a endometriose pode afetar a receptividade uterina (KLEMMT et al., 2006). Embora os estudos não sejam completamente concordantes, têm se observado na endometriose alterações no repertório de células NK, linfócitos T e macrófagos e também, nos níveis de citocinas (GM-CSF, IL-1, IL-4, IL-6, IL-8, IL-10 e TNF-α entre outras) e de fatores de crescimento (TGF-β, IGF-1, HGF e VEGF). Essas alterações podem estar associadas a mudanças no perfil do endométrio e na sua capacidade de propiciar atividade adequada por parte das

células imunológicas, vitais para o sucesso implantacional e gestacional (KRÁLÍČKOVÁ; VETVICKA, 2015).

Também foram observadas alterações nos biomarcadores da decidualização no endométrio eutópico das pacientes com endometriose (KLEMMT et al., 2006; MINICI et al., 2008). A decidualização estudada *in vitro* sob a influência do fluido peritoneal de pacientes com endometriose mostrou-se comprometida, sugerindo a influência do meio endometriótico sobre a fisiologia endometrial (MINICI et al., 2008). Em ensaios em que o TNF-α foi inibido (positivamente correlacionado com a severidade da endometriose; RICHTER et al., 2005) as alterações geradas pelo fluido endometriótico no processo de decidualização mostraram-se atenuadas, enfatizando o papel das citocinas inflamatórias na perda de qualidade do endométrio eutópico (MINICI et al., 2008).

Por outro lado, o endométrio é uma mucosa complexa, cujos componentes agem em sintonia por meio de diferentes respostas e mecanismos para permitir a implantação e desenvolvimento do embrião. Um desses componentes, muitas vezes negligenciado ou estudado de forma isolada, com intensa capacidade de resposta a alterações do meio são as células endoteliais (LUK et al., 2010). Devido a sua posição estratégica, células endoteliais endometriais estão expostas a mudanças do perfil sistêmico, seja devido a presença de patógenos ou de mediadores solúveis, como, por exemplo, os mediadores inflamatórios liberados pelas células do sistema imunológico na patologia da endometriose. As células endoteliais são também uma importante fonte de mediadores inflamatórios e quimiotáxicos, podendo responder a uma ampla gama de estímulos biológicos (SANTORO et al., 2014). Desta forma, na vigência de um processo inflamatório como se caracteriza a endometriose, estas células devem ser consideradas como parceiros endometriais ativos e relevantes.

No contexto destes achados e, a fim de contribuir com informações sobre a possível influência do ambiente endometriótico sobre a fisiologia endometrial, este estudo utilizou culturas tridimensionais de células estromais uterinas revestidas por endotélio (microambiente uterino reconstituído) para a avaliação

do perfil de citocinas em resposta ao soro de pacientes saudáveis ou com endometriose.

CONCLUSÕES

- O modelo experimental de cocultivo 3D permite mimetizar as relações estroma-capilar endometrial e, de forma mais completa do que com culturas 2D, a análise da influência do ambiente sobre a fisiologia endometrial.

- Os diferentes níveis de citocinas produzidos pelo endométrio reconstituído frente ao perfil sérico das pacientes que fazem uso ou não de anticoncepcionais, mostram a capacidade das células endometriais de responder a um perfil específico de citocinas.

- As células endometriais apresentaram uma resposta exacerbada no perfil de IL-2, IL-6, IL-10, IFN-γ e TNF-α quando expostas ao soro de mulheres com endometriose sem uso de anticoncepcionais, ou seja, com um perfil mais inflamatório, o que sugere que estas células podem contribuir com o perfil sistêmico inflamatório encontrado em mulheres com endometriose.

- Células endometriais expostas ao soro de mulheres com endometriose, porém tratadas com anticoncepcionais, apresentaram uma expressão elevada diferencial das citocina pró-inflamatória IL-6, da quimiocina IL-8 e da citocina anti-inflamatória IL-4, o que pode estar relacionado à tentativa de recrutar células imunes para o local inflamado (Tregs) e com a regulação da inflamação.

- Nossos achados sugerem que o uso de cocultivos de células estromais e endoteliais endometriais como ferramenta de estudo, ao associar a possibilidade de interações mutuas entre tipos celulares que compartilham o mesmo tecido e condições, amplia a compreensão dos mecanismos que ocorrem *in vivo*.

REFERÊNCIAS*

ABRÃO, M. S., GONÇALVES, M. O., DIAS, J. A. JR, PODGAEC, S., CHAMIE, L. P., BLASBALG, R. Comparison between clinical examination, transvaginal sonography and magnetic resonance imaging for the diagnosis of deep endometriosis. **Hum. Reprod.,** v. 22, n. 12, p. 3092 – 7, 2007.

ABRÃO, M. S., PODGAEC, S. Surgical treatment of endometriosis. In: ABRÃO, M. S. (Ed.). **Endometriosis: a contemporary vision.** Rio de Janeiro, Ed. Revinter**,** 2000. p. 67 – 78.

AHN, S. H., MONSANTO, S. P., MILLER, C., SINGH, S. S., THOMAS, R., TAYADE, C. Pathophysiology and immune dysfunction in endometriosis. **Biomed. Res. Int.,** v. 10, p. 795 - 976. 2015.

ALÌ, G., BOLDRINI, L., LUCCHI, M., PICCHI, A., DELL'OMODARME, M., PRATI, M. C., MUSSI, A., CORSI, V., FONTANINI, G. Treatment with interleukin-2 in malignant pleural mesothelioma: immunological and angiogenetic assessment and prognostic impact. **Br. J. Cancer.,** v. 101, p. 1869 – 1875, 2009.

ALTINTAS, D., KOKCU, A., TOSUN, M., CETINKAYA, M. B., KANDEMIR, B. Efficacy of recomninant human interferon alpha-2b on experimental endometriosis. **Eur. J. Obstet. Gynecol. Reprod. Biol.,** v.139, n. 1, p. 95-9, 2008.

ANTSIFEROVA, Y. S., SOTNIKOVA, N. Y., POSISEEVA, L. V., SHOR, A. L. Changes in the T-helper cytokines profile and in lymphocyte activation at the systemic and local levels in women with endometriosis**. Fertil. Steril.,** v. 84, n. 6, p. 1705 – 11, 2005.

APLIN, J. D. The cell biological basis of human implantation. **Baillieres. Best. Pract. Res. Clin. Obstet. Gynecol.,** v. 14, p. 757 – 64, 2000.

APLIN, J. D., CHARLTON, A. K., AYAD, S. An immunohistochemical study of human endometrial extracellular matrix during the menstrual cycle and first trimester of prergnancy. **Cell Tissue Res.,** v. 253, n. 1, p. 231 – 40, 1988.

ASHKAR, A. A., DI SANTO, J. P., CROY, B. A. Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy. **J. Exp. Med.,** v. 192, n. 2, p. 259-70, 2000.

AUGUST, A. D., KONG, H. J., MOONEY, D. J. Alginate hydrogels as biomaterials. **Macromol. Biosci.,** v. 8, n. 6, p. 623 – 33, 2006.

De acordo com: ASSOCIAÇÃO BRASILEIRA DE NORMAS TÉCNICAS. **NBR 6023:** informação e documentação: referências: elaboração. Rio de Janeiro, 2002.

BARMAT, L.I; NASTI, K.; YANG, X.; SPANDORFER, S.; KOWALIK, A.; EL-ROEIY, A. Are cytokines and growth factors responsible for the detrimental effects of hydrosalpingeal fluid on pregnancy rates after in vitro fertilization-embryo transfer? **Fertil. Steril.,** v. 72, n. 6, p. 1110–1112, 1999.

BARNHART, K., DUNSMOOR-SU, R., COUTIFARIS, C. Effect of endometriosis on in vitro fertilization. **Fertil. Steril.,** v. 77, n. 6, p. 1148 – 55, 2002.

BENTIN-LEY, U., LINDENBERG, S., HORN, T., LARSEN, J. F. Ultrastructure of endometrial epithelial cells in a three-dimensional cell culture system for human implantation studies. **J. Assist. Reprod. Genet.,** v. 12, n. 9, p. 632 – 8, 1995.

BENTIN-LEY, U., PEDERSEN, B., LINDENBERG, S., LARSEN, J. F., HAMBERGER, L., HORN, T. Isolation and culture of human endometrial cells in a three-dimensional culture system. **J. Reprod. Fertil.,** v. 101, n. 2, p. 327 – 32, 1994.

BERKKANOGLU, M., ARICI, A. Immunology and endometriosis. **Am. J. Reprod. Immunol.,** v. 50, n. 1, p. 48 – 59, 2003.

BERKLEY, K. J., RAPKIN, A. J., PAPKA, R. E. The pains of endometriosis. **Science,** v. 308, p. 1587 – 9, 2005.

BERSINGER, N. A., VON ROTEN, S., WUNDER, D. M., RATIO, L., DREHER, E., MUELLER, M.D. PAPP-A and osteoprotegerin, together with interleukin-8 and RANTES, are elevated in the peritoneal fluid of women with endometriosis. **Am. J. Obstet. Gynecol.,** v. 195, n. 1, p. 103-8, 2006.

BISSELL, M. J., WEAVER, V. M., LELIÈVRE, S. A., WANG, F., PETERSON O. W., SCHMEICHEL, K. L. Tissue structure, nuclear organization, and gene expression in normal and malignant breast. **Cancer Res.,** v. 59, p. 1757 – 1763, 1999.

BOYMAN, O., SPRENT, J. The role of interleukine-2 during homeostasis and activation of the immune system. **Nature Rev. Immunol.,** v. 12, p. 180 – 190, 2012.

BROSENS, J. J., PIJNENBORG, R., BROSENS, I. A. The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. **Am. J. Obstet. Gynecol.;** v. 87, p. 1416–23, 2002.

BULUN, S. E. Endometriosis. **N. Engl. J. Med.,** v. 360, p. 268 – 79, 2009.

BULUN, S. E., CHENG, Y. H., PAVONE, M. E., XUE, Q., ATTAR, E., TRUKHACHEVA, E., UTSUNOMIYA, H., YIN, P., LUO, X., LIN, Z., IMIR, G., THUNG, S., SU, E. J., KIM, J. J. Estrogen receptor-beta estrogen receptor-alpha, and progesterone resistance in endometriosis. **Semin. Reprod. Med.,** v. 28, n. 1, p. 36 – 43, 2010.

CAMPBELL, J. J., DAVIDENKO, N., CAFFAREL, M. M., CAMERON, R. E., WATSON, C. J. A multifunctional 3D co-culture system for studies of mammary tissue morphogenesis and stem cell biology. **PLoS. One,** v. 6, n. 9, p. 256 - 61 2011.

CAMPOREALE, A., POLI, V. IL-6, IL-17 and STAT3: a holy trinity in auto-immunity? **Front. Biosci.,** v. 17, n. 1, p. 2306 – 26, 2012.

CAPOBIANCO, A., ROVERE-QUERINI, P. Endometriosis, a disease of the macrophage. **Front. Immunol.,** v.28, p. 4 – 9, 2013.

CAVAZOS, F., GREEN, J. A., HALL, D. G., LUCAS, F. V. Ultrastructure of the human endometrial glandular cell during the menstrual cycle. **Am. J. Obstet. Gynecol.**, v. 99, n. 6, p. 833 – 54, 1967.

CHAMIÉ, L. P., BLASBALG, R., GONÇALVES, M. O., CARVALHO, F. M. B., ABRÃO, M. S., OLIVEIRA, I. S. Accuracy of magnetic resonance imaging for diagnosis and preoperative assessment of deeply infiltrating endometriosis. **Int. J. Gynecol. Obst.,** v. 106, n. 3, p. 198 – 201, 2009.

CHAOUAT, G., DUBANCHET, S., LEDÉE, N. Cytokines: Important for implantation? **J. Assist. Reprod. Genet.,** v. 24, n. 11, p. 491 – 505, 2007.

CHAPRON, C., CHOPIN, N., BORGHESE, B., FOULOT, H., DOUSSET, B., VACHER-LAVENU, M. C., VIEIRA, M., HASAN, W., BRICOU, A. Deeply infiltrating endometriosis: pathogenetic implications of the anatomical distribution. **Hum. Reprod.,** v. 21, p. 1839 – 45, 2006.

CHAVEZ, A. R., BUCHSER, W., BASSE, P. H., LIANG, X., APPLEMAN, L. J., MARANCHIE, J. K., ZEH, H., DE VERA, M. E., LOTZE, M.T. Pharmacologic administration of interleukin-2. **Ann. N. Y. Acad. Sci.,** v. 1182, p. 14 – 27, 2009.

CHEN, C. p., LIU, S. H.., LEE, M. Y., CHEN, Y. Y. Heparan sulfate proteoglycans in the basement membranes of the human placenta and decidua. **Placenta,** v. 29, n. 4, p. 309 – 16, 2008.

CHEN, W. J., HU, X. F., YAN, M., ZHANG, W. Y., MAO, X. B., SHU, Y. W.. Human umbilical vein endothelial cells promote the inhibitory activation of CD4(+)CD25(+)Foxp3(+) regulatory T cells via PD-L1. **Atheroscl.,** v. 244, p. 108 – 12, 2016.

CHEN, X.W., ZHOU, S.F. Iflammation, cytokines, the IL-17/IL-6/STAT3/NF-kB axis, and tumorigenesis. **Drug. Des. Devel. Ther.,** v. 9, p. 2941 – 2946, 2015.

CHENG, Y. M., WANG, S. T., CHOU, C. Y. Serum CA-125 in preoperative patients at high risk for endometriosis. **Obstet. Gynecol.,** v. 99, n. 3, p. 375 – 80, 2002.

CHIANG, C. M., HILL, J A. Localization of T cells, interferon-gamma and HLA-DR in eutopic and ectopic human endometrium. **Gynecol. Obstet. Invest.,** v. 43, n. 4, p. 245 – 50, 1997.

CHURCH, H. J., RICHARDS, A. J., JOHN, A. D. Laminins in decidual, placenta and choriocarcinoma cells. **Placenta,** v. 18, n. 2, p. 143 – 162, 1997.

COLE, L. A., LADNER, D. G., BYRN, F. W. The normal variabilities of the menstrual cycle. **Fertil. Steril.,** v. 91, n. 2, p. 522 – 7, 2009.

CORK BA, LI TC, WARREN MA, LAIRD SM. Interleukin-11 (IL-11) in human endometrium: expression throughout the menstrual cycle and the effects of cytokines on endometrial IL-11 production in vitro. **J. Reprod. Immunol.,** v. 50, n. 1, p. 3 – 17, 2001.

CORNILLIE, F. J., OOSTERLYNCK, D., LAUWERYNS, J. M., KONINCKX, P.R. Deeply infiltrating pelvic endomeriosis: histology and clinical significance. **Fertil. Steril.,** v. 52, p. 978 – 83, 1990.

CORRIGALL, V. M., ARASTU, M., KHAN, S., SHAH, C., FIFE, M., SMEETS, T., TAK, P. P., PANAYI, G. S. Functional IL-2 receptor beta (CD122) and gamma (CD132) chains are expressed by fibroblast-like synoviocytes: activation by IL-2 stimulates monocyte chemoattractant protein-1 production. **J. Immunol.,** v. 166, n. 6, p. 4141 – 7, 2001.

D'ANDREA, A., RENGARAJU, M., VALIANTE, N. M., CHEHIMI, J., KUBIN, M., ASTE, M., CHAN, S. H., KOBAYASHI, M., YOUNG, D., NICKBARG, E. Production of natural killer cell stimulatory factor (interleukin 12) by peripheral blood mononuclear cells. **J. Exp. Med.,** v. 176, n. 5, p. 1387 – 398, 1992.

DA COSTA E SILVA, R. C., MOURA, K. K., RIBEIRO, Jr., C. L., GUILLO, L. A. Estrogen signaling in the proliferative endometrium: implication in endometriosis. **Rev. Assoc. Med. Bras.,** v.62, n. 1, p. 72 – 7, 2016.

DE HONDT, A., PEERAER, K., MEULEMAN, C., MEEUWIS, L., DE LOECKER, P., D'HOOGHE, T. M. Endometriosis and subfertility treatment: a review. **Minerva Ginecol.,** v. 57, n. 3, p. 257 – 67, 2005.

DE ZIEGLER, D., PIRTEA, P., GALLIANO, D., CICINELLI, E., MELDRUM, D. Optimal uterine anatomy and physiology necessary for normal implantation and placentation. **Fertil. Steril.,** v. 105, n. 4, p. 844 – 54, 2016.

DIMITRIADIS, E., MENKHORST, E., SALAMONSEN, L. A., PAIVA, P. Review: LIF and IL11 in trophoblast-endometrial interactions during the establishment of pregnancy. **Placenta,** p. 99-104, 2010.

DIMITRIADIS, E., SALAMONSEN, L. A., ROBB, L. Expression of interleukin-11 during the human menstrual cycle: coincidence with stromal cell decidualization and relationship to leukaemia inhibitory fator and prolactina. **Mol. Hum. Reprod.,** v. 10, n. 6, p. 907 – 14, 2000.

DIMITRIADIS, E., STOIKOS, C., STAFFORD-BELL, M., CLARK, I., PAIVA, P., KOVACS, G., SALAMONSEN, L. A. Interleukin-11, IL-11 receptoralpha and leukemia inhibitory factor are dysregulated in endometrium of infertile women with endometriosis during the implantation window. **J. Reprod. Immunol.,** v. 69, n.1, p. 53 – 64, 2006.

DIMITRIADIS, E., WHITE, C. A., JONES, R. L., SALAMONSEN, L. A. Cytokines, chemokines and growth factors in endometrium related to implantation. **Hum. Reprod. Update.,** v. 11, n. 6, p. 613-630, 2005.

EIKAWA, S., OHUE, Y., KITAOKA, K., AJI, TOSHIKI, UENAKA, A., OKA, M., NAKAYAMA, E. Enrichment of Foxp3+ CD4 regulatory T cells in migrated T

cells to IL-6 and IL-8 expressing tumors through predominant induction of CXCR1 by IL6. **J. Immunol.,** v. 185, p. 6734 – 6740, 2010.

EMERMAN, J. T., PITELKA, D. R. Maintenance and induction of morphological differentiation in dissociated mammary epithelium on floating collagen membranes**. In Vitro.,** v.13, n. 5, p. 316 – 28, 1977.

ERLEBACHER, A. Immunology of the maternal–fetal interface. **Ann. Rev. Immunol.,** v. 31, p. 387-411, 2013.

ESFANDIARI, N., KHAZAEI, M., AI, J., BIELECKI, R., GOTLIEB, L., RYAN, E., CASPER, R. F. Effect of a statin on a in vitro modelo f endometriosis. **Fertil. Steril.,** v. 87, n. 2, p. 257 – 62, 2007.

EVRON, A.; GOLDMAN S.; SHALEV, E. Effect of primary human endometrial stromal cells on epithelial cell receptivity and protein expression is dependent on menstrual cycle stage. **Hum. Reprod.,** v. 26, n. 1, p. 176–190, 2011.

FERENCZY, A., RICHART, R. M. Scanning and transmission electron microscopy of the human endometrial surface epithelium. **J. Clin. Endocrinol. Metab.,** v. 36, n. 5, p. 999 – 1008, 1973.

FLUCKIGER, A. C., GARRONE, P., DURAND, I., GALIZZI, J. P., BANCHEREAU, J. Interleukin 10 (IL10) upregulates functional high affinity IL-2 receptors on normal and leukemic B lymphocytes. **J. Exp. Med.,** v. 178, n. 5, p. 1473 – 81, 1993.

GARBERS, C., SCHELLER, J. Interleukin-6 and interleukin-11: same same but different. **Biol. Chem.,** v. 394, n. 9, p. 1145 – 61, 2013.

GARRIDO, N., NAVARRO, J., GARCÍA-VELASCO, J., REMOH, J., PELLICE, A., SIMÓN, C. The endometrium versus embryonic quality in endometriosis-related infertility. **Hum. Reprod. Update.,** v. 8, n. 1, p. 95 – 103, 2002.

GIUDICE, L. C. Clinical practice. Endometriosis. **N. Engl. J. Med.,** v. 362, n. 25, p. 2389 – 98, 2010.

GIUDICE, L. C., KAO, L. C. Endometriosis. **Lancet.,** v. 364, n. 13, p. 1789-99, 2004.

GIUDICE, L. C., TELLES, T. L., LOBO, S., KAO, L. The molecular basis for implantation failure in endometriosis: on the road to discovery. **Ann. N. Y. Acad. Sci.,** v. 955, p. 252-64, 2002.

GLEISSNER, C. A., ZASTROW, A., KLINGENBERG, R., KLUGER, M. S., KONSTANDIN, M., CELIK, S., HAEMMERLING, S., SHANKAR, V., GIESE, T., KATUS, H. A., DENGLER, T. J. IL-10 inhibits endothelium-dependent T cell costimulation by up-regulation of ILT3/4 in human vascular endothelial cells. **Eur. J. Immunol.,** v. 37, n. 1, p. 177 – 92, 2007.

GMYREK, G. B., SIERADZKA, U., GOLUDA, M., GABRYS, M., SOZANSKI, R., JERZAK, M., ZBYRYT, I., CHROBAK, A., CHELMONSKA-SOYTA, A. Flow cytometric evaluation of intracellular cytokine synthesis in peripheral

mononuclear cells of women with endometriosis. **Immunol. Invest.,** v. 37, n. 1, p. 43 – 61, 2008.

GONÇALVES, M. O., DIAS, J. A. JR, PODGAEC, S., AVERBACH, M., ABRÃO, M. S. Transvaginal ultrasound for diagnosis of deeply infiltrating endometriosis. **Int. J. Gynecol. Obst.,** v. 104, n. 2, p. 156 – 60, 2009.

GONCALVES, M. O., PODGAEC, S., DIAS, J. A. JR, GONZALEZ, M., ABRAO, M. S. Transvaginal ultrasonography with bowel preparation is able to predict the number of lesions and rectosigmoid layers affected in cases of deep endometriosis, defining surgical strategy. **Hum. Reprod.,** v. 25, n. 3, p. 665 – 71, 2010.

GREENE, A. D., LANG, S. A., KENDZIORSKI, J. A., SROGA-RIOS, J. M., HERZOG, T. J., BURNS, K. A. Endometriosis: where are we and where are we going? **Reprod.,** v. 152, n. 3, p. 63 – 78, 2016.

GUZELOGLU-KAYISLI, O., KAYISLI, U. A., TAYLOR, H. S. The role of growth factors and cytokines during implantation: endocrine and paracrine interactions. **Semin. Reprod. Med.,** v. 27, p. 62 – 79, 2009.

HALME, J. Release of tumor necrosis factor-a by human peritoneal macrophages in vivo and in vitro. **Am. J. Obstet. Gynecol.,** v. 161, p. 1718 – 1725, 1989.

HARADA, T., IWABE, T., TERAKAWA, N. Role of cytokines in endometriosis. **Fertil. Steril.,** v. 76, n. 1, p. 1 – 10, 2001.

HERINGTON, J. L., BRUNER-TRAN, K. L., LUCAS, J. A., OSTEEN, K. G. Immune interactions in endometriosis. **Expert. Rev. Clin. Immunol.,** v. 7, n. 5, p. 611 – 26, 2011.

HICKEY, M., BALLARD, K., FARGUHAR, C. Endometriosis. **BMJ.,** v. 348, p. 1752, 2014.

HILL, J. A., FARIS, H. M., SCHIFF, I., ANDERSON, D. J. Characterization of leukocyte subpopulations in the peritoneal fluid of women with endometriosis. **Fertil. Steril.,** v. 50, n. 2, p. 216 – 22, 1988.

HO, H. N., WU, M. Y., CHAO, K. H., CHEN, C. D., CHEN, S. U., CHEN, H. F., YANG, Y. S. Decrease in interferon gamma production and impairment of T-lymphocyte proliferation in peritoneal fluid of women with endometriosis. **Am. J. Obstet. Gynecol.,** v. 175, p. 1236 – 1241, 1996.

HORNUNG, D., KLINGEL, K., DOHRN, K., KANDOLF, R., WALLWIENER, D., TAYLOR, R. N. Regulated on activation normal T-cell-expressed and – secreted mRNA expression in normal endometrium and endometriotic implants: assessment of autocrine/paracrine regulation by in situ hybridization. **Am. J. Pathol.,** v.158, n. 6, p. 1949-54, 2001.

HORNUNG, D., RYAN, I. P., CHAO, V. A., VIGNE, J. L., SCHRIOK, E. D., TAYLOR, R. N. Immunolocalization and regulation of the chemokine RANTES in human endometrial and endometriosis tissues and cells. **J. Clin. Endocrinol. Metab.,** v. 82, n. 5, p. 1621-8, 1997.

HSU, A. L., KHACHIKYAN, I., STRATTON, P. Invasive and noninvasive methods for the diagnosis of endometriosis. **Clin. Obstet .Gynecol.,** v. 53, n. 2, p. 413 – 9, 2010.

HULL, M. G., ARMATAGE, R. J., MCDERMOTT, A. Use of follicle-stimulating hormone alone (urofollitropin) to stimulate the ovaries for assisted conception after pituitary desensitization. **Fertil. Steril.,** v. 62, n. 5, p. 997 – 1003, 1994.

HUMRICH JY, RIEMEKASTEN G. Restoring regulation - IL-2 therapy in systemic lupus erythematosus. **Expert. Rev. Clin. Immunol.,** v. 12, n. 11, p. 1153 – 60, 2016.

JANSEN R. P., RUSSELL, P. Nonpigmented endometriosis: clinical, laparoscopic, and pathologic definition. **Am. J. Obstet. Gynecol.,** v. 155, n. 6, p. 1154 – 9, 1986.

JEE, B. C., SUH, C. S., KIM, S. H., MOON, S. Y. Serum soluble CD163 and interleukin-6 levels in women with ovarian endometriomas. **Gynecol. Obstet. Invest.,** v. 66, p. 47 – 52, 2008.

KALU, E., SUMAR, N., GIANNOPOULOS, T., PATEL, P., CROUCHER, C., SHERRIFF, E., BANSAL, A. Cytokine profiles in serum and peritoneal fluid from infertilite women with and without endometriosis. **J. Obstet. Gynaecol. Res.,** v. 33, n. 4, p.490-5, 2007.

KALVAKOLANU, D. V. Interferons and cell growth control. **Histol Histopathol.,** v. 15, p. 523 – 537, 2000.

KENNEDY, S., BERGGVIST, A., CHAPRON, C., D'HOOGHE, T., DUNSELMAN, G., GREB, R., HUMMELSHOJ, L., PRENTICE, A., SARIDOGAN, E. Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHERE guideline for the diagnosis and treatment of endometriosis. **Hum. Reprod.,** v. 20, n. 10, p. 2698-704, 2005.

KENNEDY, S., BERGQVIST, A., CHAPRON, C., D'HOOGHE, T., DUNSELMAN, G., GREB, R., HUMMELSHO,J. L., PRENTICE, A., SARIDOGAN, E. ESHRE guideline for the diagnosis and treatment of endometriosis. **Hum. Reprod.,** v. 20, p. 698 – 704, 2005.

KHORRAM O, TAYLOR RN, RYAN IP, SCHALL TJ AND LANDERS DV. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometriosis. **Am. J. Obstet. Gynecol.,** v.169, n. 6, p.1545–1549, 1993.

KING, S. M., QUARTUCCIO, S., HILLARD, T. S., INOUE, K., BURDETTE, J. E. Alginate hydrogels for three-dimensional organ culture of ovaries and oviducts. **J. Vis. Exp.,** v. 52, p. 2804, 2011.

KISALUS, L. L., HERR, J. C., LITTLE, C. D. Immunolocalization of extracellular matrix proteins and collagen synthesis in first-trimester human decidua. **Anat. Rec.,** v. 218, n. 4, p. 402 – 15, 1987.

KLEMMT, P.A., CARVER, J. G., KENNEDY, S. H., KONINCKX, P. R., MARDON, H. J. Stromal cells from endometriotic lesions and endometrium from

women with endometriosis have reduced decidualization capacity. **Fertil. Steril.,** v. 85, n.3, p. 564-72, 2006.

KOBAYASHI, H., HIGASHIURA, Y., SHIGETOMI, H., KAJIHARA, H. Pathogenesis of endometriosis: the role of initial infection and subsequent sterile inflammation (Review). **Mol. Med. Rep.,** v. 9, n. 1, p. 9 – 15, 2014.

KONINCKX, P. R., CORNILLIE, F. J. Deeply infiltrating endometriosis: a new entity. In: SHAW, R. W. (Ed.). **Endometriosis**. Carnforth. Parthenon. Publishing Group., 1990. 31 – 4.

KONINCKX, P. R., MEULEMAN, C., DEMEYERE, S., LESAFFRE, E., CORNILLIE, F. J. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain**. Fertil. Steril.,** v. 55, p. 759 – 1991.

KOYAWA, K., SHIKONE, T., NAKANO, R. Apoptosis in the Human Uterine Endometrium during the Menstrual Cycle. **J. Clin. Endoc. Metab.,** v. 81, n. 11, 1996.

KRÁLÍČKOVÁ, M., VETVICKA, V. Immunological aspects of endometriosis: a review. **Ann. Transl. Med.,** v. 3, n. 11, p. 153, 2015.

LALITKUMAR, P. G. L., LALITKUMAR, S., MENG, C. X., STAVREUS-EVERS, A., HAMBILIKI, F., BENTIN-LEY, U., GEMZELL-DANIELSSON, K. Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an in vitro endometrial three-dimensional cell culture model. **Hum. Reprod.,** v. 22, n. 11, p. 3031 – 3037,2007.

LANDGREN, B. M., JOHANNISSON, E., STAVREUS-EVERS, A., HAMBERGER, L., ERIKSSON, H. A new method to study the process of implantation of a human blastocyst in vitro. **Fertil. Steril.,** v. 65, n. 5, p. 1067 – 70, 1996.

LASKARIN, G., KAMMERER, U., RUKAVINA, D. Antigen-presenting cells and materno-fetal tolerance: an emerging role for dendritic cells. **Am. J. Reprod. Immunol.,** v. 58, p. 255-267, 2007.

LAUDAŃSKI, P., SZAMATOWICZ, J., ONISZCZUK, M. Profiling of peritoneal fluid of women with endometriosis by chemokine protein array. **Ady. Med. Sci.,** v.51, p. 148-52, 2006.

LE BOUTEILLER, P., PICCINNI, M. P. Human NK cells in pregnant uterus: why there? **Am. J. Reprod. Immunol.,** v. 59, p. 401 – 406, 2008.

LEBOVIC, D. I., MUELLER, M. D., TAYLOR, R. N. Immunology of endometriosis. **Fertil. Steril.,** v. 75, n.1, p. 1-10, 2001.

LEE, Y. H., CUI, L., FANG, J., CHERN, B. S., TAN, H. H., CHAN, J. K. Limited value of pro-inflammatory oxylipins and cytokines as circulating biomarkers in endometriosis – a targete ‘omics study. **Sci. Rep.,** v. 19, n. 6, 2016.

LEMOS, N. A., ARBO, E., SCALCO, R., WEILER, E., ROSA, V., CUNHA-FILHO, J.S. Decreased anti- Müllerian hormone and altered ovarian folicular

cohort in infertile patients with mild/minimal endometriosis. **Fertil. Steril.,** v. 89, n. 5, p. 1064 – 8, 2008.

LESSEY BA. Assessment of endometrial receptivity. **Fertil. Steril.,** v. 96, n. 3, p. 522-9, 2011.

LEVAST, B., LI, Z., MADRENAS, J. The role of IL-10 in microbiome-associated immune modulation and disease tolerance. **Cytokine,** v. 75, n. 2, p. 291- 301, 2014.

LI, T. C., ROGERS, A. W., DOCKERY, P., LENTON, E. A., COOKE, I. D. A new method of histologic dating of human endometrium in the luteal phase. **Fertil. Steril.,** v. 50, n. 1, p. 52 – 60, 1988.

LIESZ, A., KLEINSCHNITZ, C. Regulatory T cells in post-stroke immune homeostasis. **Transl. Stroke Res.,** v. 7, n. 4, p. 313 – 21, 2016.

LUISI, S., PINZAUTI, S., REGINI, C., PETRAGLIA, F. Serum markers for the noninvasive diagnosis of endometriosis. **Womens Health (Lond).,** v. 11, n. 5, p. 603 – 10, 2015.

LUK, J., SEVAL, Y., ULUKUS, M., ULUKUS, E. C., ARICI, A., KAYSLI, U. A. Regulation of monocyte chemotactic protein-1 expression in human endometrial endothelial cells by sex steroids: a potential mechanism for leukocyte recruitment in endometriosis. **Reprod. Sci.,** v. 17, n. 3, p. 278-87,2010.

LUZINA, I. G., KEEGAN, A. D., HELLER, N. M., ROOK, G. A. W., SHEA-DONOHUE, T., ATAMAS, S. P. Regulation of inflammation by interleukine-4: a review of “alternatives”. **J. Leukoc. Biol.,** v. 92, n. 4, p. 753 – 64, 2012.

MACER M. L., TAYLOR, H. S. Endometriosis and infertility: a review of pathogenesis and treatment of endometriosis - associated infertility. **Obst. Gynecol. Clin. North. Am.,** v. 39, n. 4, p. 535 – 49, 2012.

MAHUTTE, N. G., ARICI, A. New advances in the understanding of endometriosis related infertility. **J. Reprod. Immunol.,** v. 55, n. 1, p. 73 – 83, 2002.

MALUTAN, A. M., DRUGAN, T., COSTIN, N., CIORTEA, R., BUCURI, C., RADA, M. P., MIHU, D. Pro-inflammatory cytokines for evaluation of inflammatory status in endometriosis. **Cent. Eur. J. Immunol.,** v. 40, n. 1, p. 96-102, 2015.

MARCOUX, S., MAHEUX, R., BÉRUBÉ, S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. **N. Engl. J. Med.,** v. 24, n. 4, p. 217 – 22, 1997.

MARGARI, K. M., ZAFIROPOULOS, A., HATZIDAKI, E., GIANNAKOPOULOU, C., ARICI, A., MATALLIOTAKIS, I. Peritoneal fluid concentrations of β-chemokines in endometriosis. **Eur. J. Obstet. Gynecol. Rprod. Biol.,** v. 169, n. 1, p. 103-7, 2013.

MATSUZAKI, S.; DARCHA, C. Co-operation between the AKT and ERK signaling pathways may support growth of deep endometriosis in a fibrotic microenvironment in vitro. **Hum. Reprod.,** v. 30, n. 7, p. 1606-16, 2015.

MEINERT, M., ERIKSEN, G. V., PETERSEN, A. C., HELMING, R. B., LAURENT, C., ULDBJERG, N., MALMSTRÖM, A. Proteoglycans and hyaluronan in human fetal membranes**. Am. J. Obst. Gynecol.,** v. 184, n. 4, p. 679 – 685, 2001.

MEULEMAN, C., VANDENABEELE, B., FIEUWS, S., SPIESSENS, C., TIMMERMAN, D., D'HOOGHE, T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. **Fertil. Steril.,** v. 92, n. 1, p. 68-74, 2009.

MIER-CABRERA, J., GONZÁLEZ-GALLARDO, S., HERNÁNDEZ-GUERRERO, C. Effect of nitric oxide and TH1/TH2 cytokine supplementation over ectopic endometrial tissue growth in murine model of endometriosis. **Reprod. Sci.,** v. 20, n. 11, p. 1332-8, 2013.

MILLER, J. E., AHN, S. H., MONSANTO, S. P., KHALAJ, K., KOITI, M., TAYADE, C. Implications of immune dysfunction on endometriosis associated infertility. **Oncotarget.,** v. 10, 2016.

MINICI, F., TIBERI, F., TROPEA, A., ORLANDO, M., GANGALE, M. F., ROMANI, F., CAMPO, S., BOMPIANI, A., LANZONE, A., APA, R. Endometriosis and human infertility: a new investigation into the role of eutopic endometrium. **Hum. Reprod.,** v. 23, n. 3, p. 530-7, 2008.

MJOSBERG, J., BERG, G., JENMALM, MC., ERNERUDH, J. Foxp3+ regulatory t cells and t helper 1, t helper 2, and t helper 17 cells in human early pregnancy decidua. **Biol. Reprod.,** v. 82, p. 698-705, 2010.

MOEN, M. H., STOKSTAD, T. A long-term follow-up study of women with asymptomatic endometriosis diagnosed incidentally at sterilization. **Fertil. Steril.,** v. 78, p. 773–776, 2002.

MOORE, K. W., DE WAAL MALEFYT, R., COFFMAN, R. L., O'GARRA, A. Interleukin-10 and the interleukin-10 receptor. **Annu. Rev. Immunol.,** v. 19, p. 683 – 765, 2001.

MOR, G., ABRAHAMS, V. M. Potential role of macrophages as immune regulators of pregnancy. **Reprod. Biol. Endocrinol.,** v. 2, p. 1-119, 2003.

MORI, M., BOGDAN, A., BALASSA, T., CSABAI, T., SZEKERES-BARTHO, J. The decídua-the maternal bed embracing the embryo-maintains the pregnancy. **Semin. Immunopathol.,** v. 38, n. 6, p. 635-649, 2016.

MUÑOZ, L. D., SERRAMÍA, M. J., FRESNO, M., MUÑOZ-FERNÁNDEZ, M. A. Progesterone inhibits HIV1 replication in human trophoblast cells through inhibiti on of autocrine tumornecrosis factor secretion. **J. Infect. Dis.,** v. 195, n. 9, p. 1294 – 302, 2007.

MUZES, G., MOLNAR, B., TULASSAY, Z., SIPOS, F. Changes of cytokine profile in inflammatory bowel diseases. **World. J. Gastroenterol.,** v. 18, p. 5848 – 5861, 2012.

NA, Y.J., LEE, D.H., KIM, S. C., JOO, J. K., WANG, J. W., JIN, J. O., KWAK, J. Y., LEE, K. S. Effects of peritoneal fluid from endometriosis patients on the release of monocytes-specific chemokines by leukocytes. **Arch. Gynecol. Obstet.,** v. 283, n. 6, p. 1333-41, 2011.

NAKANISHI, K., YOSHIMOTO, T., TSUTSUI, H., OKAMURA, H. Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. **Cytok. Growth Fact. Rev.,** v. 12, p. 53–72, 2001.

NASH, D. M., SHELDON, I. M., HERATH, S., LANE, E. A. Endometrial explant culture to study the response of equine endometrium to insemination. **Reprod. Domest. Anim.,** v. 45, n. 4, p. 670 – 6, 2010.

NASH, D., LANE, E., HERATH, S., SHELDON, I. M. Endometrial explant culture for characterizing equine endometritis. **Am. J. Reprod. Immunol.,** v. 59, n. 2, p. 105 – 17, 2008.

NILOFF, J. M., KNAPP, R. C., SCHAETZL, E., REYNOLDS, C., BAST, R. C. JR. CA125 antigen levels in obstetric and gynecologic patients. **Obstet. Gynecol.,** v. 64, p. 703 – 707, 1984.

NISENBLAST, V., BOSSUYT, P. M., SHAIKH, R., FARQUHAR, C., JORDAN, V., SCHEFFERS, C. S., MOL, B. W., JOHNSON, N., HULL, M. L. Blood biomarkers for the non-invasive diagnosis of endometriosis. **Cochrane Database Syst. Rev.,** v. 5, 2016.

NISENBLAT, V., PRENTICE, L., BOSSUYT, P. M., FARQUHAR, C., HULL, M. L., JOHNSON, N. Combination of the non-invasive tests for the diagnosis of endometriosis. **Cochrane Database Syst. Rev.,** v. 7, 2016.

NISOLLE, M., DONNEZ, J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. **Fertil. Steril.,** v. 68, n. 4, p. 585 – 96, 1997.

NNOAHAM, K. E., HUMMELSHOJ, L., WEBSTER, P., D´HOOGHE, T., DE CICCO NARDONE, F., DE CICCO NARDONE, C., JENKISON, C., KENNEDY, S. H., ZONDERVAN, K. T. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. **Fertil. Steril.,** v. 96, n. 2, p. 366 – 373, 2011.

NORWITZ, E. R., SCHUST, D. J., FISHER, S. J. Implantation and survival of early pregnancy. **N. Engl. J. Med.,** v. 345, n. 19, p. 1400-8, 2001.

NOVAL RIVAS, M. CHALITA, T. A. Regulatory T cells in allergic diseases. **J. Allergy Clin. Immunol.,** v. 138, n. 3, p. 639 – 52, 2016.

NOYES, R. W., HERTIG, A. T., ROCK, J. Dating the endometrial biopsy. **Am. J. Obstet. Gynecol.,** v.122, n. 2, p. 262 – 3, 1975.

NYNG, Y. LIU, B., HAN, B., GUO, J., LIU, X., FAN, G., GUO, C., WANG, F., ZHOU, J., YIN, L. Analysis of influence of inflammatory factor in patients with ovarian endometriosis follicular fluid on the outcome of *in vitro* fertilization. **Zhonghua Yi Xue Za Zhi.,** v. 95, n. 47, p. 3829 – 32, 2015.

OBERG, H. H., WESCH, D., GRÜSSEL, S., ROSE-JOHN, S., KABELITZ. D. Differential expression of CD126 and CD130 mediates different STAT-3 phosphorylation in CD4+CD25- and CD25high regulatory T cells. **Int. Immunol.,** v. 18, n. 4, p. 555 – 63, 2006.

OHTAKE, H., KATABUCHI, H., MATSUURA, K., OKAMURA, H. A novel in vitro experimental model for ovarian endometriosis: the three-dimensional culture of human ovarian surface epithelial cells in collagen gels. **Fertil. Steril.,** v. 71, n. 1, p. 50 – 5, 1999.

OLIVEIRA, C. M. B., SAKATA, R. K., ISSY, A. M., GEROLA, L. R., SALOMÃO, R. Cytokines and pain. **Rev. Bras. Anestesiol.,** v. 61, n. 2, p. 255 – 265, 2011.

OPOIEN, H. K., FEDORCSAK, P., BYHOLM, T., TANBO, T. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. **Reprod. Biomed. Online**, v. 23, n. 3, p. 389 – 95, 2011.

OSUGA, Y., KOGA, K., HIROTA, Y., HIRATA, T., YOSHINO, O., TAKETANI, Y. Lymphocytes in endometriosis. **Am. J. Reprod. Immunol.,** v. 65, n. 1, p. 1 – 10, 2011.

OTHAMAN, EeL-D., HORNUNG, D., SALEM, H. T., KHALIFA, E. A., El-METWALLY, T. H., Al-HENDY, A. Serum cytokines as biomarkers for nonsurgical prediction of endometriosis. **Eur. J. Obstet. Gynecol. Reprod. Biol.,** v. 137, n. 2, p. 240 – 6, 2008.

OUYANG, W., LIAO, W., LUO, C. T., YIN, N., HUSE, M., KIM, M. V., PENG, M., CHAN, P., MA, Q., MO, Y., MEIJER, D., ZHAO, K., RUDENSKY, A. Y., ATWAL, G., ZHANG, M. Q., LI, M. O. Novel Foxo1-dependent transcriptional programs control T(reg) cell function. **Nature,** v. 491, n. 7425, p. 554 – 9, 2012.

OZAWA, A., TADA, H., TAMAI, R.,UEHARA, A., WATANABE, K., YAMAGUCHI, T., SHIMAUCHI, H., TAKADA, H., SUGAWARA, S. Expression of IL-2 receptor _ and _ chains by human gingival fibroblasts and up-regulation of adhesion to neutrophils in response to IL-2. **J. Leukoc. Biol.,** v. 74, n. 3, p. 352 – 9, 2003.

PELLICER, A., ALBERT, C., MERCADER, A., BONILLA-MUSOLES, F., REMOHI, J., SIMON, C. The follicular and endocrine environment in women with endometriosis: local and systemic cytokine production. **Ferti.l Steril.,** v. 70, p.425–431, 1998.

PITTAWAY, D. E., FAYEZ, J. A. The use of CA-125 in the diagnosis and management of endometriosis. **Fertil. Steril.,** v. 46, n. 5, p. 790 – 5, 1986.

PLAISANCE, S., RUBINSTEIN, E., ALILECHE, A., SAHRAOUI, Y., KRIEF, P., AUGERY-BOURGET, Y., JASMIN, C., SUAREZ, H., AZZARONE, B.

Expression of the interleukin-2 receptor on human fibroblasts and its biological significance. **Int. Immunol.,** v. 4, n. 7, p. 739 – 46, 1992.

PLAKS, V., BIRNBERG, T., BERKUTZKI, T., SELA, S., BEN YASHAR, A., KALCHENKO, V., MOR, G., KESHET, E., DEKEL, N., NEEMAN, M., JUNG, S. Uterine DCs crucial for decidua formation during embryo implantation in mice. **J. Clin. Invest.,** v. 118, p. 3954 – 3965, 2008.

PODGAEC, S., ABRÃO, M. S. Endometiosis: diagnosis and treatment actual aspects. **Rev. Bras. Medic.,** v. 6, n. 1, 2004.

PODGAEC, S., ABRÃO, M. S., DIAS, J. A. Jr., RIZZO, L. V., de OLIVEIRA, R. M., BARACAT, E. C. Endometriosis: and inflammatory disease with a Th2 immune response componente. **Hum. Reprod.,** v. 22, n. 5, p. 1373 – 9, 2007.

PODGAEC, S., DIAS JUNIOR, J. A., CHAPRON, C., OLIVEIRA, R. M., BARACAT, E. C., ABRÃO, M. S. Th1 and Th2 immune responses related to pelvic endometriosis. **Ver. Assoc. Med. Bras.,** v. 56, n. 1, p. 92-8, 2010.

PODOR, T. J., JIRIK, F. R., LOSKUTOFF, D. J., CARSON, D. A., LOTZ, M. Human endothelial cells produce IL-6. Lack of responses to exogenous IL-6. **Am. N. Y. Acad. Sci.,** v. 1989, n. 557, p. 374 – 85, 1989.

QUENBY, S., FARQUHARSON, R. Uterine natural killer cells, implantation failure and recurrent miscarriage. **Reprod. Biomed.,** v. 13, n. 1, p. 24-8, 2006.

RICHTER, O. N., DORN, C., RÖSING, B., FLASKAMP, C., ULRICH, U. Tumor necrosis factor alpha secretion by peritoneal macrophages in patients with endometriosis. **Arch. Gynecol. Obstet.,** v. 271, n. 2, p. 143-7,2005.

ROSE-JOHN, S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. **Int. J. Biol. Sci.,** v. 8, p. 1237 – 1247, 2012.

ROWLEY, J. A., MADLAMBAYAN, G., MOONEY, D. J. Alginate hydrogels as synthetic extracellular matrix materials. **Biomaterials,** v. 20, n. 1, p. 45 – 53, 1999.

SALAMONSEN, L. A., DIMITRIADIS, E., JONES, R. L., NIE, G. Complex regulation of decidualization: a role for cytokines and proteases--a review. **Placenta.,** v. 24, p. 76-85, 2003.

SAMPSON, J. A. Metastic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation. **Am. J. Pathol.,** v. 3, n. 2, p. 93 – 110, 1927.

SANTORO, L., D'ONOFRIO, F., CAMPO, S., FERRARO, P. M., FLEX, A., ANGELINI, F., FORNI, F., NICOLARDI, E., CAMPO, V., MASCILINI, F., LANDOLFI, R., TONDI, P., SANTOLIQUIDO, A. Regression of endotelial dysfunction in patients with endometriosis after surgical treatment: a 2-year follow-up study. **Hum. Reprod.,** v. 29, n. 6, p. 1205-10, 2014.

SARAIVA, M., O'GARRA, A. The regulation of IL-10 production by immune cells. **Nature. Rev. Immunol.,** v. 10, p. 170 – 181, 2010.

SATYASWAROOP, P. G., WARTELL, D. J., MORTEL, R. Distribution of progesterone receptor, estradiol dehydroprogesterone dehydrogenase activities in human endometrial glands and stroma: progestin induction of steroid dehydrogenase activities in vitro is restricted to the glandular epithelium. **Endocrinol.**, v. 111, n. 3, p. 743 – 9, 1982.

SEMINO, C., SEMINO, A., PIETRA, G., MINGARI, M. C., BAROCCI, S., VENTURINI, P. L., RAGNI, N., MELIOLI, G. Role of major histocompatibility complex class I expression and natural killer-like T cells in the genetic control of endometriosis. **Fertil. Steril.,** v. 64, n. 5, p. 909 – 16, 1995.

SHARPE-TIMMS, K. L. Endometrial anomalies in women with endometriosis. **Ann. N. Y. Acad. Sci.,** v. 943, p. 131-47, 2001.

SHIMADA, S., NISHIDA, R., TAKEDA, M., IWABUCHI, K., KISHI, R., ONOÉ, K., MINAKAMI, H., YAMADA, H. Natural killer, natural killer T, helper and cytotoxic T cells in the decidua from sporadic miscarriage. **Am. J. Reprod. Immunol.,** v. 56, n.3, p. 193-200,2006.

SIKORA, J., MIELCZAREK-PALACZ, A., KONDERA-ANASZ, Z., STRZELCZY, J. Peripheral blood proinflammatory response in women during menstrual cycle and endometriosis. **Cytokine,** v. 76, n. 2, p. 117 – 22, 2015.

SIMOENS, S., DUNSELMAN, G., DIRKSEN, C., HUMMELSHOJ, L., BOKOR, A., BRANDES, I., BRODSZKY, V., CANIS, M., COLOMBO, G. L., DELEIRE, T., FALCONE, T., GRAHAM, B., HALIS, G., HORNE, A., KANJ, O., KJER, J. J., KRISTENSEN, J., LEBOVIC, D., MUELLER, M., VIGANO, P., WULLSCHLEGER, M., D'HOOGHE, T. The burden of endometriosis: costs and quality of life of women with endmetriosis and treated in referral centres. **Hum. Reprod.,** v. 27, n. 5, p. 1292 – 9, 2012.

SIMON C, MARTIN JC, PELLICER A. Paracrine regulators of implantation. **Baillieres Best. Pract. Res. Clin. Obstet. Gynaecol.,** v. 14, p. 815 – 26, 2000.

STEELE, R. W., DMOWSKI, W. P., MARMER, D. J. Immunologic aspects of human endometriosis. **Am. J. Reprod. Immunol.,** v. 6, n. 1, p. 33 – 6, 1984.

STREULI, I., DE ZIEGLER, D., GAYET, V., SANTULLI, P., BIJAOUI, G., DE MOUZON, J., CHAPRON, C. In women with endometriosis anti-Müllerian hormone levels are decreased only in those with previous endometrioma surgery. **Hum. Reprod.,** v. 27, n. 11, p. 3294 – 303, 2012.

SYROP, C. H., HALME, J. Peritoneal fluid environment and infertility. **Fertil. Steril.,** v. 48, n. 1, p. 1 – 9, 1987.

TANAKA, E., SENDO, F., KAWAGOE, S., HIROI, M. Decreased natural killer cell activity in women with endometriosis. **Gynecol. Obstet. Invest.,** v. 34, n. 1, p. 27 – 30, 1992.

TARABORRELLI, S. Physiology, production and action of progesterone. **Acta. Obstet. Gynecol. Scand.,** v. 161, p. 8 – 16, 2015.

TEKLENBURG, G., MACKLON, N. S. Review: in vitro models for the study of early human embryo-endometrium interactions. **Reprod. Sci.,** v. 16, n. 9, p. 811 – 8, 2009.

TESHIMA, T., HILL, G. R., PAN, L., BRINSON, Y. S., VAN DEN BRINK, M. R., COOKE, K. R., FERRARA, J. L. IL-11 separates graft-versus-leukemia effects from graft-versus-host disease after bone marrow transplantation. **J. Clin. Inv,** v. 104, n. 3, p. 317-25, 1999.

The pratictice comitee of the american society for reproductive medicine. Endometriosis and infertility. **Fertil. Steril.,** n. 8, p. 40 – 5, 2004.

THIRUCHELVAM, U., WINGFIELD, M., O´FARRELLY, C. Natural killer cells: key players in endometriosis. **Am. J. Reprod. Immunol.,** v. 74, n. 4, p. 291 – 301, 2015.

TILBURGS, T., SCHERJON, S. A., VAN DER MAST, B. J., HAASNOOT, G. W., VERSTEEG – VDV, M. M., ROELEN, D. L., VAN ROOD, J. J.,CLAAS, F. H. Fetal-maternal Hla-C mismatch is associated with decidual T cell activation andinduction of functional t regulatory cells. **J. Reprod. Immunol.,** v.82, p. 148-157, 2009.

TREPICCHIO, W. L., BOZZA, M., PEDNEAULT, G., DORNER, A. J. Recombinant human IL-11 attenuates the inflammatory response through down-regulation of proinflammatory cytokine release and nitric oxide production**. J. Immunol.,** v. 157, n. 8, p. 3627-3634, 1996.

ULUKUS, M., CAKMAK, H., ARICI, A. The role of endometrium in endometriosis. **J. Soc. Gynecol. Investig.,** v.13, n. 7, p. 467 – 76, 2006.

VALENTIJN, A. J., SARETZKI, G., TEMPEST, N., CRITCHLEY, H. O., HAPANGAMA, D. K. Human endometrial epithelial telomerase is important for epithelial proliferation and glandular formation with potential implications in endometriosis. **Hum. Reprod.,** v. 30, n. 12, p. 2816 – 28, 2015.

VERCAMMEN E. E.; D'HOOGHE T. M. Endometriosis and recurrent pregnancy loss. **Semin. Reprod. Med.,** v. 18, n. 4, p. 363 - 8, 2000.

VERCELLINI, P., SOMIGLIANA, E., VIGANÒ, P., DE MATTEIS, S., BARBARA, G., FEDELE, L. The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review. **Acta. Obstet. Gynecol. Scand.,** v. 88, n. 10, p. 1047 – 82, 2009.

VERCELLINI, P., VIGANÒ, P., SOMIGLIANA, E., FEDELE, L. Endometriosis: pathogenesis and treatment. Nat Rev. **Endocrinol.,** n. 10, p. 261 – 75, 2014.

VIDI, P. A., BISSELL, M. J., LELIÈVRE, S. A. Three-dimensional culture of human breast ephitelial cells: the how and the why. **Methods. Mol. Biol.,** v. 945, p. 193 – 219, 2013.

VIGANÒ, P., PARAZZINI, F., SOMIGLIANA, E., VERCELLINI, P. Endometriosis: epidemiology and aetiological factors. **Best. Pract. Res. Clin. Obstet. Gynaecol.,** v. 18, n. 2, p. 177-200, 2004.

VIGANÒ, P., SOMIGLIANA, E., DI BLASIO, A. M.,COZZOLINO, S., CANDIANI, M., VIGNALI, M. Suppression of natural killer cell function and production of soluble ICAM-1: endometrial stroma versus melanoma. **Am. J. Reprod Immunol.,** v. 46, n. 5, p. 342 – 8, 2001.

VIGNALI, D. A., KUCHROO, V. K. IL-12 family cytokines: immunological playmakers. **Nat Immunol.,** v. 13, n. 8, p. 722-728, 2012.

WALMSLEY, M., BUTLER, D. M., MARINOVA-MUTAFCHIEVA, L., FELDMANN, M. An anti-inflammatory role for interleukin-11 in established murine collagen-induced arthritis. **Immunol.,** v. 95, n. 1, p. 31, 1998.

WANG, H., PILLA, F., ANDERSON, S., MARTÍNEZ-ESCRIBANO, S., HERRER, I., MORENO-MOYA, J. M., MUSTI, S., BOCCA, S., OEHNINGER, S., HORCAJADAS, J. A. A novel model of human implantation: 3D endometrium-like culture system to study attachment of human trophoblast (Jar) cell spheroids. **Mol. Hum. Reprod.,** v. 18, n. 1, p. 33 – 43, 2012.

WERBROUCK, E., SPIESSENS, C., MEULEMAN, C., D'HOOGHE, T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. **Fertil. Steril.,** v. 86, n. 3, p. 566 – 71, 2006.

WU, M. H., SHOJI, Y., WU, M. C., CHUANG, P. C., LIN, C. C., HUANG, M. F., TSAI, S. J. Suppression of matrix metalloproteinase-9 by prostaglandin E(2) in peritoneal macrophage is associated with severity of endometriosis. **Am. J. Pathol.,** v. 167, n. 4, p. 1061 – 9, 2005.

WU, M. Y., YANG, J. H., CHAO, K. H., HWANG, J. L., YANG, Y. S., HO, H. N. Increase in the expression of killer cell inhibitory receptors on peritoneal natural killer cells in women with endometriosis. **Fertil. Steril.,** v. 74, n. 6, p. 1187 – 91, 2000.

WUNDER, D. M., MUELLER, M. D., BIRKHAUSER, M. H., BERSINGER, N. A. Increased ENA-78 in the follicular fluid of patients with endometriosis. **Acta. Obstet. Gynecol. Scand.,** v. 85, p. 336 – 42, 2006.

WYNN, R. M. Ultrastructural development of the human decidua. **Am J Obstet Gynecol.,** v. 118, n. 5, p. 652 – 70, 1974.

YOSHINAGA, K. Review of factors essential for blastocyst implantation for their modulating effects on the maternal immune system. **Semin. Cell Dev. Biol.,** v. 19, p. 161 – 169, 2008.

YOVICH, J. L., MATSON, P. L., BLACKLEDGE, D. G., TURNER, S. R., RICHARDSON, P. A., YOVICH, J. M., EDIRISINGHE, W. R. The treatment of normospermic infertility by gamete intrafallopian transfer (GIFT). **Br. J. Obstet. Gynaecol.,** v. 95, n. 4, p. 361-6, 1988.

ZHANG, G., TSANG, C. M., DENG, W., YIP, Y. L., LUI, V. W., WONG, S. C., CHEUNG, A. L., HAU, P. M., ZENG, M., LUNG, M. L., CHEN, H., LO, K. W., TAKADA, K., TSAO, S.W. Enhanced IL-6/IL-6R signaling promotes growth and malignant properties in EBV-infected premalignant and cancerous nasopharyngeal epithelial cells. **PLoS One.,** v. 8, n. 5, p. 622 – 84, 2013.

ZHANG, J. M., AN, J. Cytokines, inflammation, and pain. **Int. Anesthesiol. Clin.,** v. 45, p. 27 – 37, 2007.