Diplomarbeit

Endometriosis and the pro-inflammatory cytokine milieu

eingereicht von

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zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

Lehrstuhl für Pharmakologie

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Graz, 30.10.2019

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Graz, am 30.10.2019 *Umar Fouz eh.*

Acknowledgements

At this point, I would like to thank all those who supported and motivated me during the preparation of this diploma thesis.

First of all, I would like to thank PD Mag. Dr. Petra Luschnig, who supervised and reviewed my diploma thesis. For the helpful comments and the constructive criticism during the course of this thesis I would like to thank you very much.

I would also like to thank my sister who was at my side with a lot of patience, interest and helpfulness. Thanks also to my brother for times of fun and distraction.

Finally, I would like to thank my parents, who made my studies possible by their support and have always given me the confidence not to give up even in difficult times.

Zusammenfassung

Hintergrund: Endometriose ist eine einschränkende und chronische gynäkologische Erkrankung, von der fast zehn Prozent der Frauen weltweit betroffen sind. Bei dieser Erkrankung setzt sich endometriumähnliches Gewebe in verschiedenen Körperregionen ab, das zyklische Symptome wie z.B. Dysmenorrhö und chronische Symptome wie z.B. Unfruchtbarkeit verursachen kann. Die Ursachen der Endometriose scheinen multifaktoriell zu sein und sind noch nicht vollständig geklärt. Ein Faktor in der Pathogenese dieser Krankheit ist die immunologische Dysfunktion, wovon das Zytokinsystem im speziellen Gegenstand dieser Arbeit ist. Zytokine sind wichtige Signalmoleküle und spielen eine entscheidende Rolle bei der Regulierung von Entzündungsprozessen.
Methoden: Eine PubMed-Suche wurde mit den Stichworten "Endometriose", "Zytokine", "Diagnose", "Biomarker", Therapie" durchgeführt und die Referenzen in den gefundenen Artikeln ebenfalls überprüft. Darüber hinaus wurden relevante Lehrbücher in englischer und deutscher Sprache herangezogen.
Ergebnisse: Zytokine spielen eine wesentliche Rolle bei der Entstehung von Entzündungsprozessen im Zusammenhang mit der endometriotischen Implantation. Sie tragen auch zum Erhalt der Implantate bei, indem sie die Blutgefäßbildung in ihrer Umgebung induzieren und die Immunreaktion auf das neu implantierte Gewebe deaktivieren. Darüber hinaus sind sie für die Erhöhung des Schweregrades der Endometriose verantwortlich, da sie mit mehreren Symptomen und Komplikationen der Krankheit verbunden sind.
Im Hinblick auf die Diagnose wurden Veränderungen im Zytokinspiegel in Peritonealflüssigkeit, peripherem Blut und endometrialem/endometriotischem Gewebe im Vergleich zu gesunden Kontrollen festgestellt.
Schlussfolgerungen: Basierend auf diesen Veränderungen können Zytokine Teil eines Biomarker-Screening-Tests für Endometriose werden, der die heutige invasive und kostspielige Methode zur Identifizierung der Krankheit ersetzen könnte. In Bezug auf die Therapie könnten Zytokine und ihre verwandten Wege ein neues Ziel für Medikamente darstellen, die das Fortschreiten der Erkrankung unterdrücken oder Symptome wie Schmerzen, Unfruchtbarkeit und Adhäsionsbildung bei Frauen mit Endometriose behandeln.

Eine weitere Aufklärung des Mechanismus von Zytokinen bei der Endometriose könnte zu neuen Strategien in der Diagnose und Behandlung der Endometriose führen, die Patientinnen helfen könnten, eine bessere Lebensqualität zu erreichen.

Abstract

Background: Endometriosis is a debilitating and chronic gynecologic disease that affects almost ten percent of women worldwide. In this disease, endometrial-like tissue manifests itself in different parts of the body causing cyclical symptoms, like dysmenorrhea, as well as chronic symptoms, like infertility. The causes of endometriosis seem to be multifactorial and are still not fully understood. One factor in the pathogenesis of this disease is immunologic dysfunction, of which the cytokine system is the subject of this thesis. Cytokines are important signal molecules and play a crucial role in regulating inflammatory processes.

Methods: A Pubmed search was conducted with the keywords ‘endometriosis’, ‘cytokines’, ‘diagnosis’, ‘biomarker’, therapy’ and references within identified papers were also reviewed. In addition, relevant textbooks in both English and German language were used.

Results: Cytokines play an essential role in causing inflammatory processes associated with endometriotic implantation. They also contribute to the sustainment of the implants by inducing blood vessel formation in their environment and by deactivating immune reaction to the newly attached tissue. Furthermore, they are responsible for increasing the severity of endometriosis as they are associated with several symptoms and complications of the disease. With regard to diagnostics, cytokine levels in peritoneal fluid, peripheral blood and endometrial/endometriotic lesions were found to be changed compared with healthy controls.

Conclusions: Based on these changes, cytokines may become part of a biomarker screening test for endometriosis that could replace today’s invasive and costly way of identifying the disease. With regard to therapy, cytokines and their related pathways may present a new target for medication that suppresses disease progression or treats symptoms, like pain, infertility and adhesion formation in women with endometriosis.

Further illumination of the biomechanism of cytokines in endometriosis might lead to new strategies in diagnosis and treatment of endometriosis that can help patients to achieve a better quality of life.

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1 Introduction

1.1 Definition and history of endometriosis

The term endometriosis is composed of the words “endometrium”, i.e. the mucous tissue forming the inner lining of the uterine cavity and “osis”, i.e. abnormal condition. Endometriosis is clinically characterized as the presence of endometrial-like tissue in ectopic locations, which is outside of the uterine cavity (Brosens and Benagiano, 2011).
Endometriosis can affect different organs. I) *Endometriosis genitalis interna* characterizes a type of endometriosis that affects the myometrium, also known as adenomyosis uteri, as well as a kind of endometriosis in the uterine end of the fallopian tubes. II) *Endometriosis genitalis externa* by contrast, describes a variety of endometriosis occurring in the female genital tract outside the uterus and in the peritoneum, including vulva, vagina, tuba uterina, sacro-uterine ligaments, douglas pouch, perineum, and ovaries. The latter location is also called endometrioma, and often forms so-called chocolate or tar cysts. III) The *endometriosis extragenitalis* refers to lesions in the retroperitoneum, bladder, intestines, belly button, ureter and less frequent in places further away from the lower abdomen, like the brain, peripheral nerves, bones, liver, lungs or skin. Iatrogenic causes may also lead to scar endometriosis after surgery (Ärzteblatt Redaktion Deutsches, 2010).
The ectopic endometrial tissue is liable to hormonal influences of the female reproductive cycle and is able to cause abdominal pain, dysmenorrhea, dyspareunia, gastrointestinal and urological disorders as well as infertility (Bulun, 2009).

First morphological records of endometriosis can be traced back to 1690. Table 1 gives a historical overview on the scientific discovery of the disease.

Date	**Event**
1690	First morphological record of an endometriosis by Daniel Shroen in Jena.
1739	Johann Crell in Wittenberg describes an ovarian endometrioma for the first time.

1860/61	Outside the ovaries endometriosis is described by Karl Freiherr von Rokitansky as adenomyoma in Vienna.
1896	Friedrich von Recklinghausen and Thomas Cullen work independently on the adenomyomas and adenomyosis.
1899	Johannes Pfannenstiel characterizes rectovaginal endometriosis.
1912	The term "adenomyosis" is introduced by O. Frank.
1921	John A. Sampson introduces the transplantation theory (retrograde menstruation).
1932	Lauches describes estrogen dependence of the disease. R. Meyer makes a morphological characterization of the disease. He calls it adenomyohyperlasia interna uteri.
1925-32	The term "endometriosis" is used to describe the disease.
1937-39	Theories on causes by Philipp and Huber.
1950s	Development of further biochemical and endocrine concepts.
From 1970s to date	Development of molecular and immunological concepts.
From 1998 to date	Tissue-Injury-And Repair concept is introduced by G. Leyendecker.
From 2000 to date	The concepts of tissue array, gene expression arrays, genomics, proteomics are developed.

Table 1: Historical overview (Ebert, 2014, p.2)

1.2 Epidemiology

Overall, endometriosis is found in around one tenth of all childbearing-aged women (Houston, 1984). In women with infertility, endometriosis has been diagnosed up to 50% (Eskenazi and Warner, 1997), and in women with pelvic pain the diagnosis rate can further reach up to 70% (Carter, 1994).
In absolute numbers, it is figured that 176 million women over the world suffer from the disease (Adamson, Kennedy and Hummelshoj, 2010).
Houston and coworkers reported that the incidence rate of endometriosis is about 2% (Houston, 1984).

In the majority of women with endometriosis, symptoms start during pubescence, but the diagnosis of endometriosis lasts on average 6 - 7 years (E. C. Dun *et al.*, 2015)(Nnoaham *et al.*, 2011).

Endometriosis seems to be associated with reproduction-related factors, such as nulliparity, menarche at earlier age, menopause at later age, polymenorrhagia and more frequent menstrual cycles. In addition, lifestyle factors like lower body weight and alcohol or caffeine use also seem to increase disease risk (Sangi-Haghpeykar and Poindexter, 1995)(Matalliotakis *et al.*, 2008)(Grodstein *et al.*, 1993). Otherwise, African race, multiple births, history of oral contraceptives use, smoking, higher body mass index, and intake of omega-3 fatty acids are factors that have been reported to decrease risk of endometriosis (Missmer *et al.*, 2004)(Vercellini *et al.*, 2011)(Missmer *et al.*, 2010).

Risk factors	**Factors leading to decreased risk**
Early onset of menarche	Births
Short duration menstrual cycle	Oral Contraceptives
Lower Body weight	Smoking
Alcohol intake	Lower BMI
Caffeine intake	Omega-3 Fatty Acids

Table 2: Risk factors of endometriosis (Parasar, Ozcan and Terry, 2017)

1.3 Cardinal symptoms and manifestations

The symptoms of endometriosis are numerous, and their intensity depends more on the localisation of the endometriotic lesions than on the stage of the disease.

1.3.1 Symptoms of pain

There are five main symptoms of endometriosis that are reported by up to 80% of endometriosis patients. These are pelvic pain, dysmenorrhea, dyspareunia, dysuria and dyschezia, all of which are associated with pain.
The degree of pain varies greatly from one woman to another as it depends on several factors, such as the type, quantity and location of endometriotic lesions and the depth of invasion (Howard, 2009).

Possible mechanisms to explain these pains are:

- nerve damage caused by endometriotic lesions
- inflammatory reaction following cyclical micro-bleeding of the lesions
- the formation of adhesions which cause painful inner deformations or pulling of the peritoneum
- production of PGE_2, $PGF_{2\alpha}$, pro-inflammatory cytokines by endometriotic lesions

Accordingly, the pain may be cyclical or persistent (Howard, 2009).

Pelvic Pain
Pelvic pain is found in about 40% of endometriosis patients and manifests itself when there is deep intestinal damage.
The pain may be abdominal, pelvic, lumbar or sacral and intensifies during ovulation or menstruation. It can be explained by damage to the digestive tract and adhesive deformations which are caused by endometriotic lesions (Adamson, 2012).

Secondary dysmenorrhea
Dysmenorrhea is convulsive pain in the lower abdomen before, during or after menstruation due to increased intrauterine pressure. It is the most frequent symptom of endometriosis and may impair the affected woman to such an extent that her daily-life activity become infeasible. Dysmenorrhea can induce pain that radiates into the back and legs, nausea, vomiting, and as well fainting spells. It may start several days before menstruation, increases in intensity during the first two days of bleeding and persist for several days afterwards. In contrast to primary

dysmenorrhea, which occurs soon after the first menstruation in adolescent women and is not due to an organic disease, secondary dysmenorrhea does not occur until adulthood, when endometriosis starts to manifest itself (Ebert, 2014, p. 29).

Dyspareunia

Dyspareunia refers to pain during or after coitus. It is increased in the second part of the menstrual cycle and reflects the damage caused by endometriotic lesions to the uterosacral ligaments, the Douglas pouch and recto-vaginal septum. During coitus this damaged tissue is stretched, causing the pain (Ebert, 2014, p.29).

Dysuria

Painful urination and bladder incontinence during menstruation are frequent symptoms of endometriosis. They occur when endometriotic lesions that are located in the bladder roof are strained when the bladder is filled (Ebert, 2014, p.30).

Dyschezia

Painful defecation is another symptom experienced by endometriosis patients. It can occur during menstruation only or persist in later stages of the disease. It is usually caused by endometriotic infiltration of the rectum or sigmoid. Other intestinal symptoms can be intestinal bleeding, flatulence, tenesmus, stomach pain and inappetence (Ebert, 2014, p.30).

1.3.2 Manifestations

Adhesions

Adhesions (Figure 1) are a typical manifestation of active peritoneal endometriosis. They are caused by fibrin exudation and subsequent fibrinolysis as part of an inflammatory response to endometriotic lesions. Adhesions are mostly formed in the vicinity of the ovaries, between ovaries and tubes, in the Douglas pouch and in the uterovesical pouch. By attaching the tubes and ovaries to each other and to the nearby structures, they can mechanically prevent the uptake of the ovum by the fimbriae and lead to involuntary childlessness. In addition, they can be

responsible for chronic, non-cyclical pelvic pain by drawing on the richly innervated peritoneum (Diamond and Shavell, 2012).

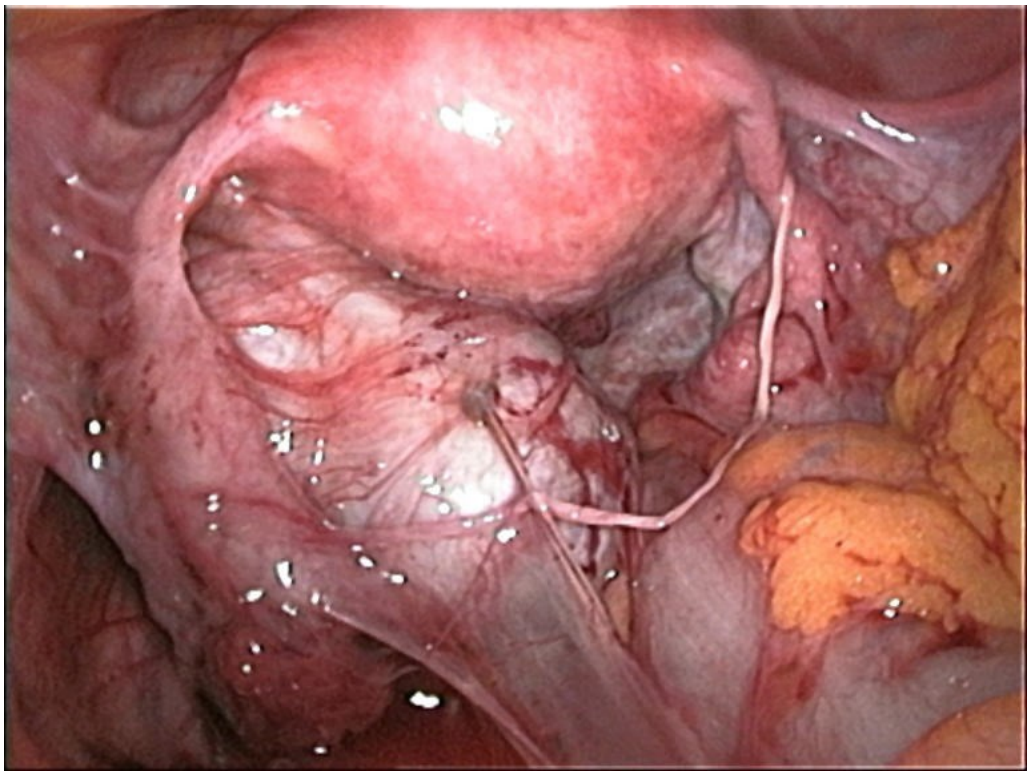

Fig. 1: Massive adhesions in endometriosis
(Hic et nunc (https://commons.wikimedia.org/wiki/File:Endometriosis2.jpg), „Endometriosis2“, marked as public domain)

Sterility/Infertility

Infertility describes the inability to maintain a viable pregnancy despite non-problematic conception, while sterility is the impossibility of conception. About half of women with endometriosis are affected. The cause may be adhesions or occlusion of the tubes due to endometriotic implants. Ovulation may not occur or transport of sperms and ovum may be impeded by dysfunctional uterine movement. Other possible mechanisms may be autoimmune processes and reduced oocyte quality (Ebert, 2014).

Table 3 provides an overview of the frequencies of the symptoms of endometriosis.

Symptom	**Frequency**
Dysmenorrhea	58-80%
Pelvic pain	40-50%
Infertility	50%

Dyspareunia	45%
Dysuria	1-2%
Dyschezia	1-2%

Table 3: Frequency of endometriosis symptoms (Gupta, Harlev and Agarwal, 2015)

The intensity of the pain can be measured according to the score developed by Biberoglu and Behrman in 1981, as depicted in the following table.

Symptoms	**Degree**	**Criteria**
Dysmenorrhea	Severe	In bed one or more days. Incapacitation
	Moderate	In bed part of day, occasional loss of work
	Mild	Some loss of work efficiency
Dyspareunia	Severe	Avoids intercourse because of pain
	Moderate	Intercourse painful to point of interruption of intercourse
	Mild	Tolerated discomfort
Pelvic Pain	Severe	Requires strong analgesis, persistent during cycle other than during menstruation
	Moderate	Noticeable discomfort for most of cycle
	Mild	Occasional pelvic discomfort
Pelvic tenderness	Severe	Unable to palpate because of tenderness
	Moderate	Extensive tenderness on palpitation
	Mild	Minimal tenderness on palpitation
		No tenderness
Induration	Severe	Nodular adnexa and cul-de-sac, uterus frequently frozen
	Moderate	Thickened and indurated adnexa and cul-de-sac, restricted mobility
	Mild	Uterus freely mobile, induration in the cul-de-sac

Table 4: Score for the intensity of endometriosis symptoms (Reprinted from Biberoglu and Behrman, 1981 with permission from Elsevier)

1.4 Clinical Anatomy

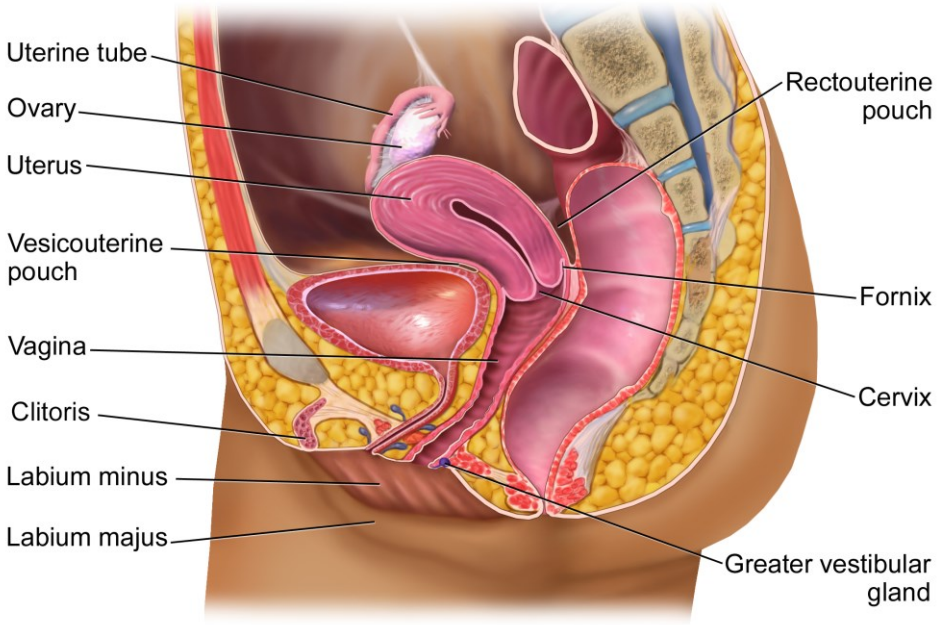

Fig. 2: Possible Sites of endometriosis
(Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436. (https://commons.wikimedia.org/wiki/File:Blausen_0400_FemaleReproSystem_02.png), „Blausen 0400 FemaleReproSystem 02“, title “The female reproductive system” removed by U.F., https://creativecommons.org/licenses/by/3.0/legalcode)

Endometriosis genitalis interna

Endometriosis genitalis interna affects the uterus and/or the fallopian tubes (Halis, Mechsner and Ebert, 2010).

In case of the involvement of the uterus, endometrial tissue grows into the outer myometrium lining and often causes an enlargement of the uterus. This condition is also called adenomyosis uteri which could be accompanied with typical symptoms like hypermenorrhea, dysmenorrhea and dyspareunia (Halis, Mechsner and Ebert, 2010). At the same time, endometriosis can also affect the fallopian tubes. In this case, endometriotic tissue grows into the interstitial area of the tubes and causes a thickening knot, which is also called salpingitis isthmica nodosa. Involvement of the tubes may lead to complete obstruction, causing hematosalpinx and infertility (Halis, Mechsner and Ebert, 2010).

Endometriosis genitalis externa

Endometriosis genitalis externa is defined as endometriosis of various organs in the little pelvis apart from the uterus. The most common sites are ovaries, douglas

pouch and sacro-uterine ligaments. Other rarely affected sites involve vagina, vulva, perineum and rotunda ligaments (Mettler and Schmutzler, 2007). Endometriosis of the ovary refers to ectopic tissue located on the ovaries. This tissue may bleed and become invaginated into the ovary leading to the formation of cysts, which are also called endometriomas. Retained blood inside the cysts results in a thick viscous brownish type of fluid, giving them the name "chocolate cysts". Symptoms that may occur are dysmenorrhea and chronic pelvic pain . Vaginal lesions are usually found in the vaginal vault or at the portio. They can occur either in isolation or associated with a deep infiltration of the rectovaginal septum. In the latter case enhanced pain symptoms are typical due to the extensive spread (Mettler and Schmutzler, 2007).

Endometriosis extragenitalis

Endometriosis extragenitalis characterizes endometriotic lesions outside of the peritoneum. Affected sites may include the urinary tract, gastrointestinal tract, respiratory tract, retroperitoneum, skin, lungs and brain. General symptoms are dysfunction, pain and cyclic bleeding of the affected organs (Veeraswamy *et al.*, 2010).

The urinary tract, specifically the bladder, is a common site of endometriosis. It is found in about one fifth of patients with endometriosis and causes symptoms like dysuria, hematuria and urgency. In the gastrointestinal tract, frequent manifestation sites are the rectosigmoid, appendix, small bowel and rectum. Sometimes, the endometriotic tissue grows through to the intestinal mucosa, which leads to cyclic intestinal bleedings. Other symptoms that can arise are pain and defecation problems independent of the cycle (Veeraswamy *et al.*, 2010).

Rarely, endometriosis can manifest itself in the skin of the umbilical region, either through peritoneal lesions nearby or as a result of a laparoscopy. Cyclic bleeding to the outside and pain in this area may occur. Occasionally, ectopic tissue occurs in surgery-related scars, e.g. after caesarean sections. Endometriosis of the pleura has also been reported, associated with severe cyclic chest pain and leading to spontaneous pneumothorax and cyclical hemoptysis (Veeraswamy *et al.*, 2010).

Location	Frequency
Cul-de-Sac	61%
Right broad ligament	38%
Right uterosacral ligament	37%
Left uterosacral ligament	35%
Left broad ligament	32%
Bladder	19%
Left ovary	14%
Fundus	11%
Sigmoid	12%
Right ovary	13%
Left tube	4%
Left round ligament	3%
Right tube	2%
Right abdominal wall	1%

Table 5: Frequency of endometriotic foci in the pelvic cavity (Redwine, 1987)

1.5 Etiology/Pathogenesis

Since the causes of endometriosis are still insufficiently comprehended, there are three main theories which are dominating in the literature: 1) retrograde menstruation, 2) coelomic metaplasia, and 3) hematogenous and lymphatic metastasis. In addition to these theories, there are among other factors the concepts of altered immunity, hormonal effects and apoptosis inhibition to explain the pathogenesis of endometriosis (Schenken, 1989).

1.5.1 Retrograde menstruation

The model of endometriosis that is currently seen by the scientific community as most probable is the hypothesis of retrograde menstruation. In this particular case it is assumed that endometrial tissue flows in an opposite direction through the fallopian tubes and subsequently implants in extra-uterine sites (Giudice and Kao, 2004). This theory was proposed for the first time by John Sampson in 1927. While

he was carrying out laparotomy on his patients during their menses, he witnessed the free flow of menstrual fluid from the fallopian tubes into the pelvic cavity. He also observed distinct lesions on the peritoneum and hypothesized that endometrial cells in the menstrual outflow might implant in peritoneal mesothelium, thus creating these lesions (Sampson, 1927b). In fact, menstruation reflux seems to be a frequent phenomenon among healthy women (Sasson and Taylor, 2008). However, this theory is corroborated by evidence that shows women with endometriosis maintain greater volumes of refluxed blood during menses compared to controls (Koninckx, 1994). Furthermore, in primate models, such as macaques and baboons, endometriosis is inducible when autologous menstrual products are inoculated into peritoneal cavity or when the cervix is blocked to prevent antegrade menstrual flow (Harirchian *et al.*, 2012) (D'Hooghe, 1997). Definitely, women with outflow tract obstruction show a higher incidence of endometriosis as described by Nunley et al. (Nunley and Kitchin, 1980).
On the other hand, this theory seems to fall short since endometriosis was also found in pre-pubertal girls as well as males, and what is more, sometimes endometriotic lesions appear at sites that are unapproachable by menstrual reflux, such as organs outside the peritoneal cavity like the lungs (Machairiotis *et al.*, 2013).

1.5.2 Coelomic metaplasia

Robert Meyer introduced the theory that endometriosis may evolve locally out of coelomic epithelium, which is a common progenitor of peritoneal and endometrial tissue (Meyer, 1924). Specifically, he postulates that the peritoneal serosa and the ovarian epithelium may transdifferentiate into endometrial tissue through metaplasia, as a consequence to inflammation or hormonal processes (Cullen, 1896)(MEYER, 1903)(Novak, 1931).
The metaplasia theory seems to be supported by the detection of elevated serum levels of coelom-associated antigen CA-125 among women with endometriosis (Pittaway and Douglas, 1989).
Moreover, coelomic metaplasia could give an explanation for endometriosis in pre-menarche aged girls, women who have undergone total uterotomy (Metzger *et al.*, 1991), postmenopausal women and ectopic lesions in extraperitoneal sites

(Suginami, 1991). Furthermore, metaplasia could give an explanation for the mechanism of the formation of deep infiltrating endometriosis (DIE) (Matsuzaki and Darcha, 2012).
However, there are some observations that contradict the coelomic metaplasia hypothesis. As a consequence of the hypothesis, one would expect endometriotic lesions to occur in an evenly distributed manner in the entirety of the abdominal cavity, and not, as it is really the case, primarily within the organs of the lesser pelvis. Moreover, one would expect incidence of endometriosis to rise with increasing age, as is usually the case with metaplasia diseases. Finally, one would expect a higher rate of lungs endometriosis, since the pleura tissue also emerges from coelomic epithelium and also a more frequent occurrence in men (Nap, 2012).

1.5.3 Induction

The induction model is a modification of the abovementioned coelomic metaplasia theory. It states that undifferentiated cells in the body are stimulated by endogenous substances to transform into endometriotic tissue. These factors are suspected to be produced by the endometrium and then travel through blood and lymph vessels to different parts of the body, inducing endometriosis. This theory is based on observations made in experiments on rabbits that endometrial tissue which has been implanted in ectopic tissues induced an endometrial-like epithelial differentiation within a few days (Levander and Normann, 1955). However, these changes did not completely correspond to endometriosis because they did not exhibit endometrial stroma (Nap, 2012).

1.5.4 Embryonic cell rests

This theory has been proposed by Recklinghausen and Russel in the 1890s (Von Recklinghausen, 1896)(Russell, 1899). It postulates that endometriosis develops from cells originating from the Mullerian ducts. This theory might offer an explanation to the frequent occurrence of endometriosis in the douglas pouch, the sacro-uterine ligaments and the broad ligament of the uterus. Furthermore, the fact that women with Mullerian anomalies were reported to have an increased

incidence of endometriosis seems to be in favor of this hypothesis (Nawroth *et al.*, 2006).

1.5.5 Lymphatic and hematogenous metastasis

The metastasis theory attempts to explain the occurrence of endometriosis in parts of the body that distant from the uterus or pelvis, including brain, lungs, pericardium, and spinal cord (Machairiotis *et al.*, 2013). Endometrial tissue may migrate from the uterine lining by the hematogenous or lymphatic way through sentinel lymph nodes and lymphatic vessels and veins to peripheral sites (Sampson, 1927a). Additionally, another theory proposes that stem cells from the bone marrow could be transported through blood vessels and so they are able to reach ectopic sites (Pluchino and Taylor, 2016).

1.5.6 Hormonal effects

Endometriotic lesions seem to have a higher responsiveness to estrogen (Augoulea *et al.*, 2012).
Dioxin and other environmental toxins which mimic estrogens could therefore enhance formation of endometriosis (Barbosa *et al.*, 2011). Furthermore, endometriotic lesions in contrast to normal endometrium show an overexpression of aromatase, an enzyme that converts androgenic precursor molecules into estradiol. Expression of aromatase is stimulated by PGE_2, which in its turn is stimulated by estradiol. This positive feedback mechanism may contribute substantially to the maintenance and progression of endometriosis (Bulun *et al.*, 2004).
Moreover, endometriotic lesions show a reduced expression of 17β-hydroxysteroid dehydrogenase, which is an enzyme that regulates the transformation of estradiol to estrone. Its decreased expression leads to a further accumulation of estradiol in ectopic lesions and consequently to an enhancement of the feedback loop described above (Bulun *et al.*, 2010).
Another point is that progesterone acts as an antagonist to estrogen-driven proliferation in the healthy endometrium but in endometriosis however, endometrial tissue shows resistance to progesterone. This resistance could be

explained either due to a decreased expression or a dysfunctionality of progesterone receptors (Patel *et al.*, 2017).

1.5.7 Immune dysfunction

The flow of menstrual debris into the peritoneum induces an inflammation that could hinder the immune system from detecting and removing endometrial cells. Women with endometriosis are known to have altered immune parameters (STEELE, Dmowski and MARMER, 1984). NK-cell levels and cellular immunity are reduced in endometriosis patients, while activated macrophages and leukocytes are increased (Oosterlynck *et al.*, 1992).
In addition endometriotic lesions may further survive by actively masking themselves to the immune-system through the expression of immunomodulatory proteins such as ICAM-1 that prevents elimination through immune-cells (Vigano *et al.*, 1998).
Moreover, ectopic cells produce growth factors and cytokines that stimulate angiogenesis. Lebovic and colleagues were able to show increased levels of proinflammatory cytokines and growth factors in patients with endometriosis compared to healthy controls (Lebovic, Mueller and Taylor, 2001).

1.5.8 Genetic factors

Apoptosis is a crucial factor in the development of endometriosis since anti-apoptotic genes are upregulated and apoptotic genes are suppressed in the endometrial tissue of women with endometriosis. This alteration could be a reason for the persistence of endometriotic cells (Evans-Hoeker *et al.*, 2016).
To date, no distinct scheme of inheritance for endometriosis has been found. However, first-degree relatives of endometriosis patients show a higher disease incidence, which hints to the involvement of genetic factors. It has been found that the risk of endometriosis is increased up to seven times among first-degree relatives versus non-relatives. Moreover, it was shown that direct relatives were much more likely to develop a severe manifestation of endometriosis than patients without known family history. Several genetic linkage studies were able to identify chromosome loci that were identical in both patients with the disease and their

first-degree relatives. Meanwhile, the endometriosis-associated genes have been identified. They include the EMX2 gene, an important transcription factor for the development of the reproductive tract, and PTEN, a tumor suppressor gene that promotes malign transformation in ovarian endometriosis (Hansen and Eyster, 2010).

1.6 Morphology

Endometriotic tissue can be distinguished with respect to biological history, pigmentation and fibrosis into atypical or red, typical or black, and old lesions (Wiegerinck, Van Dop and Brosens, 1993).

Atypical lesions refer to red hemorrhagic implants (Figure 3). These are fresh lesions resulting from a recent implantation of endometriotic cells. They come in form of flaming-red spots, small polyps, glandular efflorescence and petechiae. Additionally, they can occur as small, clear vesicles, discolored peritoneal areas and star scars. Fresh lesions are biologically active and exhibit a highly vascularized stroma, high mitotic activity, and signs of inflammation. The shedding of endometriotic cells from red lesions can lead to further implantation elsewhere in the peritoneal cavity, in the same way as a metastatic process. Red lesions are susceptible to spontaneous involution, stabilization or further transformation to the typical, blue-black lesions (Wiegerinck, Van Dop and Brosens, 1993).

Due to the cyclic activity of the red foci, there is a continuous proliferation, secretory transformation and rejection of endometriotic material, causing inflammation and scarring in the surrounding tissue. Over the time this leads to an increased fibrosis and a reduced blood supply. Subsequently, the red lesions diminish over the course of disease and turn into the characteristic blue or black lesions (Figure 4). The blue-black lesions have the form of nodules or vesicles filled with old blood and endometrial tissue and are encircled with a variable amount of fibrotic tissue. According to their appearance they are also called ‘gun-shot’ lesions (Wiegerinck, Van Dop and Brosens, 1993).

Occasionally, the increasing inflammatory and fibrotic processes can lead to a complete devascularization of the endometriotic focal point. Thus, collagenous white or brown lesions (Figure 5) are formed that represent old, biologically inactive forms of endometriotic tissue. The white-brown lesions do not cause symptoms and can be regarded as spontaneous healing (Wiegerinck, Van Dop and Brosens, 1993).

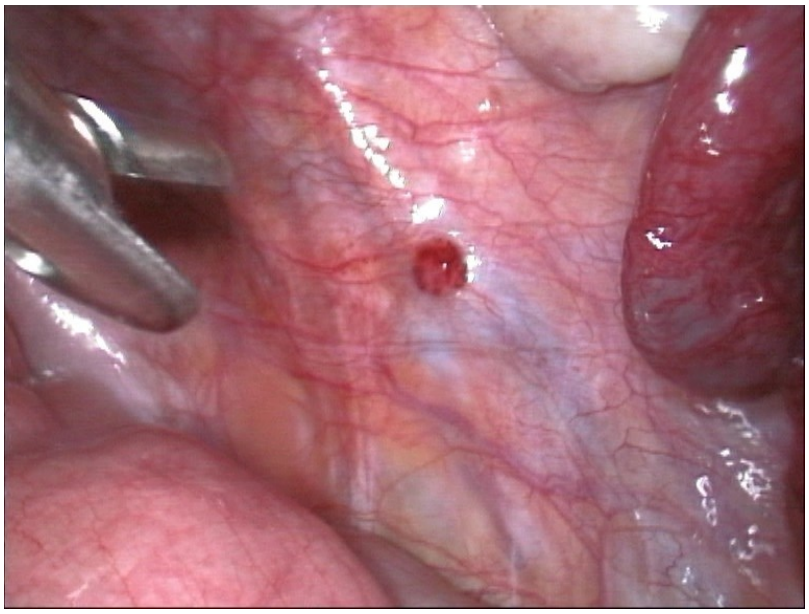

Fig. 3: Endometriotic red lesion
(Hic et nunc (https://commons.wikimedia.org/wiki/File:Red_endometriosis.jpg), „Red endometriosis“, https://creativecommons.org/licenses/by-sa/3.0/legalcode)

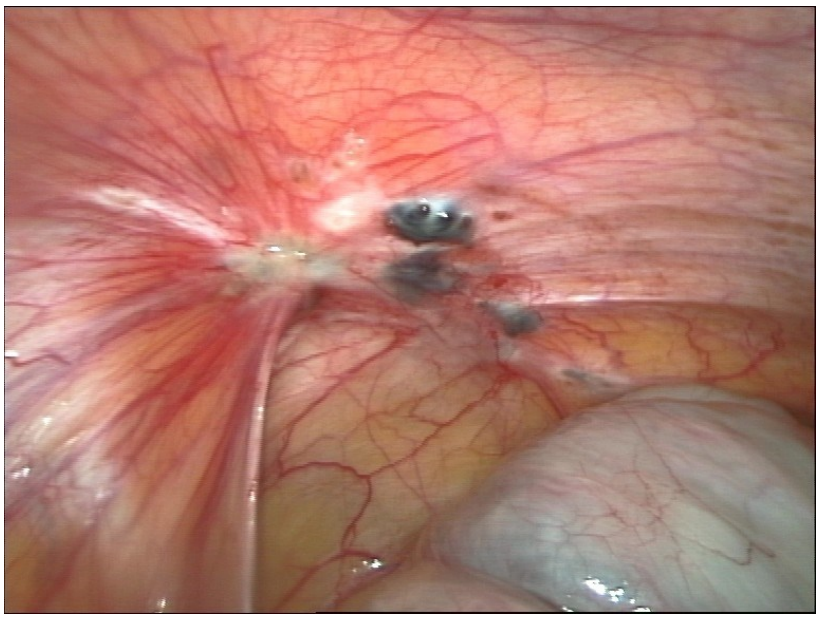

Fig. 4: Endometriotic blue-black lesions with whitish fibrosis
(Hic et nunc (https://commons.wikimedia.org/wiki/File:Extragenital_endometriosis.jpg), „Extragenital endometriosis“, https://creativecommons.org/licenses/by-sa/3.0/legalcode)

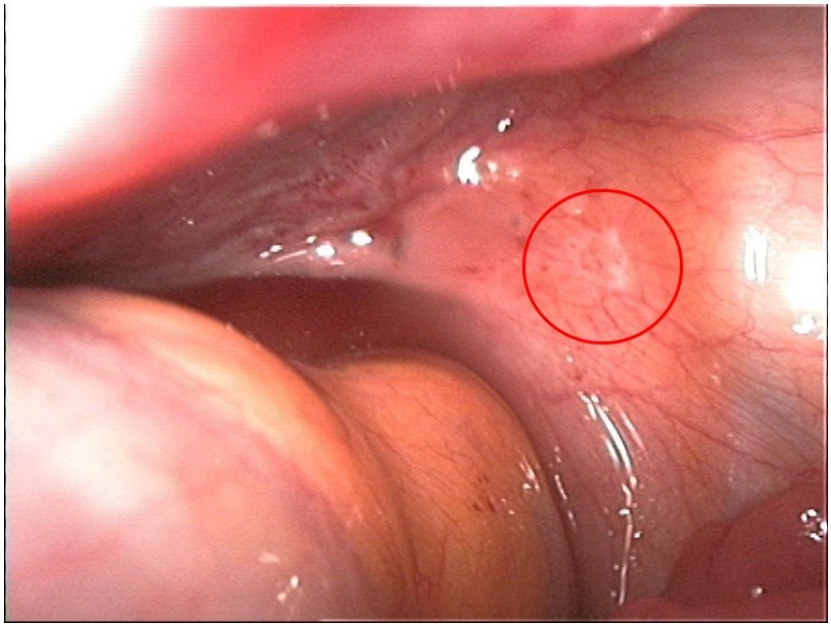

Fig. 5: Endometriotic white lesion
(Hic et nunc (https://commons.wikimedia.org/wiki/File:White_endometriosis.jpg), „White endometriosis“, https://creativecommons.org/licenses/by-sa/3.0/legalcode)

1.7 Classification

Two common systems of classification for endometriosis are the American Society for Reproductive Medicine (ASRM) classification and the Endoscopic Endometriosis Classification (EEC).
The ASRM has classified endometriosis into four stages depending on location, number, and invasiveness of the lesions and also on the type of the adhesions (Table 2) (‘Practice bulletin no. 114: management of endometriosis’, 2010).

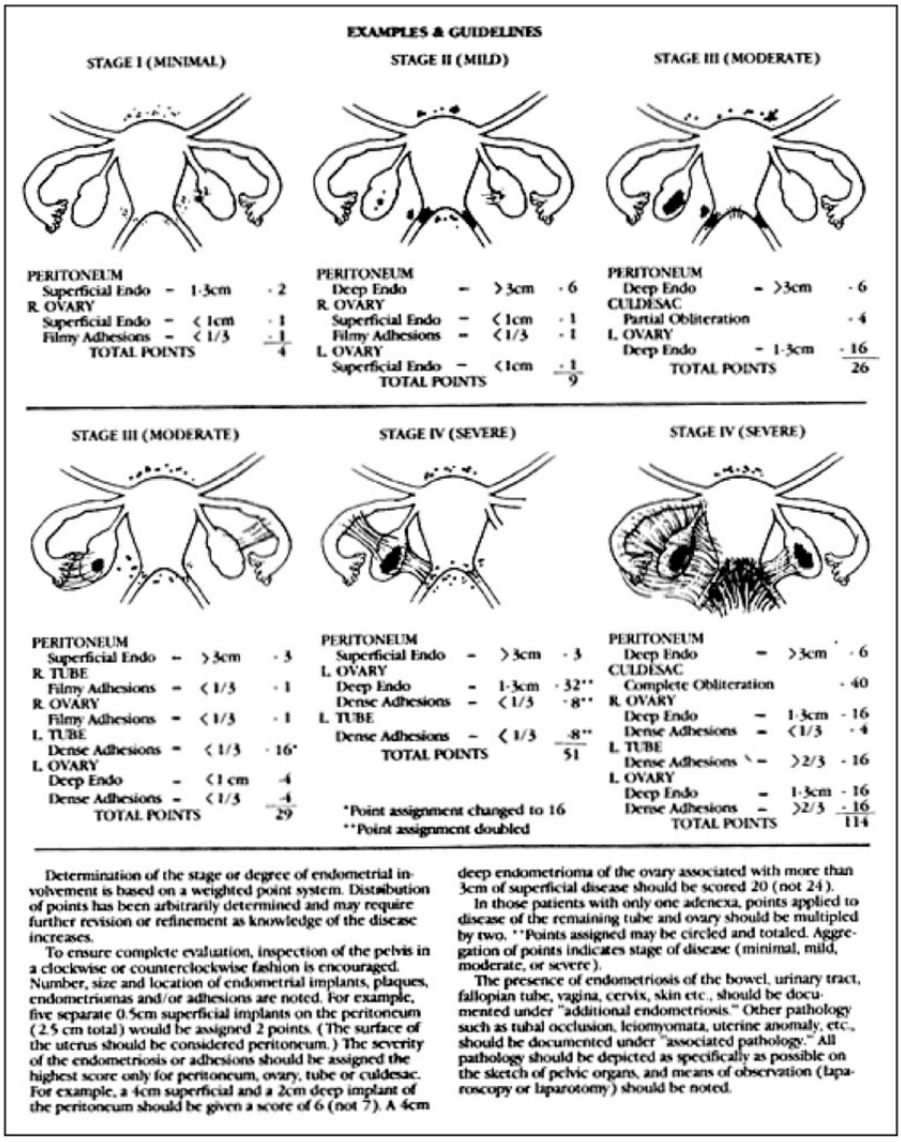

Fig. 6: Revised American Society for Reproductive Medicine classification of endometriosis: 1996 (Reprinted from 'Fertility and Sterility' with permission from Elsevier)

The EEC has also classified endometriosis into four stages. In addition, extragenital endometriotic foci are included into this classification.

Stage	**Description**
EEC 1	Size of endometriotic lesions up to 5 mm.
EEC 2	Size of endometriotic lesions greater

	than 5 mm. Blood in the Douglas pouch. Incipient adhesions between tubes, ovaries and uterus. Bleeding in ovaries.
EEC 3	Adhesions in the lesser pelvis. Large endometriomas with ovarian cysts and partial hemorrhages. Endometriotic lesions in bladder and sacro-uterine ligaments. Possible endometriotic lesions in the rectovaginal septum.
EEC 4	Endometriosis in the intestines, bladder, appendix, navel, liver, lungs, etc. with frequent monthly bleeding.

Table 6: EEC classification of endometriosis (Mettler and Schmutzler, 2007)

1.8 Diagnostics

Initial diagnosis of endometriosis is generally done on the basis of clinical history. The patient should be asked questions about (Gambone *et al.*, 2002):

- age, menstrual and pregnancy history (parity, abortions, curettages)
- dysmenorrhea (duration, intensity, bed confinement, incapacity for work, coping strategies)
- dyspareunia
- bowel movement (menstruation-dependent pain and/or changing stool consistency, blood)
- dysuria

- previous operations (doctor's letters, surgery protocols)
- medication anamnesis (contraceptives, pain medication)
- alcohol abuse
- social anamnesis (partnership, conflicts, occupational stress)
- family anamnesis (accumulation of carcinomas, endometriosis)
- frequent genital infections

The record of medical history is followed by inspection and colposcopy of the vulva, vagina and portio. Especially intravaginal and retrocervical lesions can be detected in this step (Parasar, Ozcan and Terry, 2017). Thereafter, a physical examination is conducted. It should include palpation for consistency and posture of the uterus, cystic tumors in the adnexes, nodules and tenderness in the uterosacral ligament and douglas pouch, as well as tumors in the pelvis (Parasar, Ozcan and Terry, 2017).

Since pelvic pain is the most frequent symptom in endometriosis patients and it could also be the result of many other diseases, other causes need to be ruled out. This would be done by relevant diagnostics like Papanicolaou test, pregnancy test, urine test, swab tests of the vagina and cervix (Parasar, Ozcan and Terry, 2017).

Transvaginal sonography is carried out to identify endometriomas, adenomyosis uteri, bladder lesions, and intestine lesions. Additionally, transabdominal sonography, MRI and CT are used to rule out the presence of pelvic tumors (Kennedy *et al.*, 2005)(Bazot *et al.*, 2009).

For all the afore-mentioned preliminary tests, laparoscopic examination with histologic confirmation remains the gold standard for a decisive diagnosis of endometriosis (Hsu, Khachikyan and Stratton, 2010).

1.9 Therapy

The treatment of endometriosis is an interdisciplinary process consisting of a medical treatment to relieve pain as well as suppress disease activity and a surgical excision of endometriotic lesions (Strauss, Janni and Maass, 2009).

Medical Treatment

Pain management is done according to the WHO scheme with non-steroidal anti-inflammatory drugs, COX inhibitors, weak opioids, and antidepressants. In addition, oral contraceptives are often used (Strauss, Janni and Maass, 2009). Treatment with hormones aims at depriving endometriotic lesions from the estrogenic stimulus that is necessary for their persistence and growth. Goals of hormonal therapy are reduction or elimination of lesions and symptoms and preventing recurrence of disease. Substances that are used and their respective functions are (Strauss, Janni and Maass, 2009):

- Combined oral contraceptive pills to inhibit the secretory conversion and bleeding of the endometriotic tissue
- Progestogens for the inhibition of the pituitary gonadotropin secretion and ovarian hormone production
- GnRH agonists to induce a “postmenopausal state” by suppressing gonadotropin secretion in the pituitary
- Androgen derivatives to suppress pituitary gonadotropin secretion, create hyperandrogenic state and lead to atrophy of lesions
- Aromatase inhibitors to reduce estrogen levels (Strauss, Janni and Maass, 2009)

Surgical treatment

Indications for surgical treatment of endometriosis are pain and infertility. Laparoscopy is the first line surgical method, as it is associated with a faster recovery and fewer complications. However, larger endometriotic lesions may require a laparotomic approach. Superficial lesions can be removed by coagulation or laser vaporization, while invasive lesions or extended adhesions can be resected. Endometriomas are peeled off, while preserving the ovaries. In case of an adenomyosis uteri, the most effective therapeutic method is hysterectomy, but patients with desire to have children may as well be treated conservatively with

progestins and GnRH analogues to produce an amenorrhoeic state (Lasch and Fillenberg, 2017).

Supplementary treatment and aftercare

A lot of patients with endometriosis experience an alleviation of symptoms and an improved quality of life by applying complementary therapeutics. These include traditional chinese medicine, acupuncture, physiotherapy, osteopathy, homeopathy and ayurveda.

In some cases of chronic endometriosis, patients may have to undergo further rehabilitation therapies and a follow-up treatment in specialized facilities (Lasch and Fillenberg, 2017).

1.10 Cytokines: types and functions

Cytokines are a functional group of polypeptides and proteins with a low molecular weight and short half-lifes. They are expressed or secreted by a multitude of cells. These include lymphocytes, monocytes, macrophages, endothelial cells, fibroblasts, keratinocytes, hepatocytes, thymus cells and smooth muscle cells. Generally speaking, cytokines act as mediators of intercellular communication and exert regulatory effects on cell functions via specific receptors. Cytokine effects can be mediated through autocrine, paracrine, juxtracrine and endocrine signaling, via cell surface receptors or soluble receptors. In particular, cytokines regulate immune defense against viruses, immune responses, intercellular communication between leucocytes, chemotaxis, and cell growth and differentiation (Gressner and Arndt, 2013)(Dembic, 2015).

Common characteristics of most cytokines are

1) Pleiotropy: A cytokine exerts more than one function, e.g. IL-6 promotes differentiation of osteoclasts and proliferation of keratocytes.
2) Redundancy: The same function is exerted by different cytokines. For example, IL-1β, TNF-α and IL-32 stimulate macrophages.
3) Acting as part of cascades in synergy with or in balance against other cytokines.

Currently, up to 200 cytokines are known. According to their main functions, cytokines can be classified into ***immunologic cytokines***, subdivided into interleukins, interferons, chemokines, TNF-superfamily, and ***growth factor cytokines***, subdivided into a general and a hematopoietic group. Moreover, with a special focus on immunoregulatory functions cytokines can be categorized into pro- and anti-inflammatory cytokines, examples are shown in Table 8(Gressner and Arndt, 2013).

Pro-inflammatory cytokines	Anti-inflammatory cytokines
IL-1, IL-6, IL-8, IL-12, IL-18, IFN-γ, TNF	IL-4, IL-10, IL-11, IL-13, TGF-β

Table 7: Pro- and anti-inflammatory cytokines (Gressner and Arndt, 2013)

Immunologic Cytokines

Interleukins, interferons, chemokines and the TNF superfamily can be described as immunologic cytokines. Interleukins and interferons act primarily as regulators of proliferation, differentiation and function of immune cells. Chemokines function as messenger molecules to attract immune cells into inflamed sites (Dembic, 2015).

Interleukins

The term interleukin is derived from its firstly reported function that is "to mediate between leukocytes". Interleukins are mostly glycosylated proteins with molecular weights of 8-70 kD. Until now, more than 30 interleukins have been characterized. They are produced by immune cells as well as endothelial cells and act as mediators within the immune system (Akdis *et al.*, 2016).

Interferons

Interferons are a group of proteins that exert antiviral and antiproliferative effects. They also play a regulatory role in immune responses. Interferons can be divided into two groups according to their functions.

- Interferon type I: IFN-α and IFN-β with predominantly antiviral effect
- Interferon type II: IFN-γ as an important mediator of general inflammatory response (Dembic, 2015)

Chemokines

Chemokines, which stands for chemotactic cytokines, are messenger substances that orchestrate leukocytes to the site of inflammation. Furthermore, they promote leukocyte migration out of the peripheral blood and lymphocyte migration into secondary lymphatic organs. Thus, they are involved in the initiation of inflammatory reactions. According to the arrangement of cysteine residues in their sequence, chemokines are classified into four subtypes: CX3C-, CXC-, XC-, and CC-chemokines which members all interact with G protein-coupled receptors (Dembic, 2015).

TNF Super Family

The TNF superfamily consists of peptides that interact with the TNF-receptor superfamily. Their functions are the regulation of immune responses and the apoptosis of cells. Additionally, they play a role in development and homeostasis of some tissue types, such as lymphatic, neuronal or ectodermal tissues (Dembic, 2015).

Cytokines as growth factors

Cytokines do not only have immunologic functions, but are also involved in promoting growth of human cells and tissue (Dembic, 2015).

General growth factors

General growth factors are regulators of cell proliferation, differentiation and apoptosis. Furthermore, they promote the regeneration of damaged tissue and the growth of capillaries and nerves.
These factors include the fibroblast growth factor (FGF), the epidermal growth factor (EGF), the vascular epidermal growth factor (=VEGF) and the insulin-like growth factors (IGF-1 and 2) (Dembic, 2015).

Hematopoietic growth factors

Hematopoietic growth factors are cytokines that regulate the formation and differentiation of different blood cells. They include the stem cell factor (SCF),

granulocyte colony stimulating factor (G-CSF), erythropoietin (EPO) and thrombopoietin (THPO) (Dembic, 2015).

Table 6 provides an overview of a selection of cytokines, as well as some of their producing and target cells and their main functions.

Interleukins	**Secreting cells**	**Target cells**	**Effects**
IL-1	Monocytes/ macrophages, T-, B- and NK-cells, granulocytes, epithelial cells, fibroblasts	T- and B-cells, monocytes, granulocytes, hepatocytes	Proinflammatory cytokine; fever, acute phase reaction; cell activation and induction of effector functions; promotes hematopoiesis
IL-2	T-cells	T- and B-cells, monocytes, granulocytes	T-cell activation, clonal expansion, induction of apoptosis, differentiation of cytotoxic T-cells, activation of NK- and B-cells as well as monocytes and granulocytes
IL-3	Activated T-cells, mast cells, granulocytes	Hematopoietic stem cells and progenitor cells, granulocytes, monocytes, mast cells	Synergy with IL-5 and GM-CSF for myeloid cell proliferation and differentiation
IL-4	T-cells	B-, T- and NK-cells, monocytes, progenitor cells, mast cells	B cell activation, amplification of IgG1 and IgE expression, regulation of CD23 expression on cells and monocytes, induction of TH2 response, growth factor for mast cells
IL-5	T-cells, mast cells, eosinophile granulocytes	Eosinophile and basophile granulocytes	Regulation of eosinophile expansion und chemotaxis
IL-6	T- and B-cells, monocytes,	B-, T- and NK-cells, thymocytes	Proinflammatory cytokine; acute phase reaction; broad effects on cell growth, differentiation and activation; osteoclast activation
IL-7	Bone marrow and thymus stromal cells	B-, T-cells, thymocytes	T-cell development, regulation of peripheral T-cell homeostasis and

			expansion, survival of memory cells
IL-8	T-cells, monocytes, granulocytes	T- and B-cells, mast cells and thymocytes	Mediator of acute inflammation, leukocyte activation, chemotaxis and adhesion
IL-9	T-cells	T-, B-cells, monocytes and thymocytes, progenitor cells	Growth and differentiation of mast cells, production of T-cell cytokines, production of B-cell IgE and maturation of eosinophils, oncogenesis
IL-10	T-cells and mast cells, keratinocytes, monocytes,	T-, NK- and B-cells, mast cells and monocytes	Limits inflammation through effects on monocytes, inhibits interleukin-12 and regulates growth and differentiation of B-, T- and NK-cells as well as mast cells and granulocytes
IL-11	bone marrow stromal cells	Bone marrow progenitor cells, dendritic cells, monocytes and granulocytes	Stimulation of hematopoiesis and regulation of macrophage proliferation and differentiation
IL-12	B-cells and Granulocytes	Monocytes, macrophages, B-cells, dendritic cells	Proinflammatory cytokine, induction of Th1 immune response; induces production of IFN-γ and other cytokines of NK and T cells, connects innate and adaptive immunity.
IL-13	T-cells	B-cells	Cell proliferation and switching (IgE), amplificates expression of adhesion molecules and MHC class II on monocytes/macrophages, activation of eosinophils and mast cells
IL-14	T-cells, malign B-cells	T-, B- and NK-cells, monocytes, endothelial cells, mast cells und granulocytes	Induction of B cell proliferation: inhibition of immunoglobulin secretion and selective expansion of B cell subpopulations
IL-15	Macrophages, stromal cells, monocytes	CD4 T-cells, monocytes	T cell proliferation and maturation as well as survival of memory T cells,

			inhibition of T cell apoptosis; NK cell development, function and survival
IL-16	T-cells	T cell lines, macrophages, neutrophils, granulocytes	Regulation of CD4 T-cell activation and regulation of the change from an immune to an inflammatory response
IL-17	T-cells	Stromal cells and fibroblasts	Proinflammatory cytokine, chemokine properties for neutrophils; regulation of hematopoiesis
IL-18	Keratinocytes, activated macrophages	B-, T- and NK-cells	Promotes T and NK cell maturation, IFN-γ production and cytolytic properties, may enhance Th1 or Th2 response depending on cytokine milieu
IL-27	Activated antigen-presenting cells	CD4 cells	Possibly early Th1 induction
IL-37	Monocytes and organs (uterus, testicles, thymus, tonsils, plasma cells)	Innate immunity, dendritic cells	Regulation of innate immunity, upregulation of immune responses and inflammation, inhibition of IL-18
Type I interferon: IFN-α and IFN-β	Monocytes, macrophages, B- and NK-cells	Dendritic cells and NK cells, monocytes	Antiviral effects, regulation of innate and adaptive immunity, upregulation of MHC expression
Type II interferon: IFN-γ	T cells, NK cells	T-, B cells, monocytes, NK cells	Cell activation and differentiation, upregulation of MHC expression, enhancement of cytolytic activity, selection of AK isotype
CCL2 / MCP-1	Activated Monocytes, endothelial cells	Monocytes, neutrophile granulocytes	Supports monocyte tumorstatic activity; involved in psoriasis, rheumatoid arthritis and atherosclerosis
CCL3 / MIP-1a	Activated Macrophages	Monocytes, granulocytes,T-cells	Adhesive effects on lymphocytes; inhibits the proliferation of hematopoietic stem cells

CCL4 / MIP-1b	Activated Macrophages	Monocytes, granulocytes,T-cells	Adhesive effects on lymphocytes
CCL5 / RANTES	Activated T-Cells, blood platelets	Granulocytes, T-cells	Release of histamine from basophils; activates eosinophils
CCL11 / Eotaxin	Activated endothelial cells	Eosinophil granulocytes	Recruits and activates inflammatory leukocytes; involved in the development of allergic responses.
CCL16 / Monotactin-1	Liver cells, Spleen cells	Monocytes, T-cells	Myelosuppressive activity
CCL19 / MIP-3b	Thyme, Lymph nodes	Dendritic cells, T-cells, hematopoietic progenitor cells	Expressed in lymphoid tissues; upregulated by inflammatory processes or downregulated by the anti-inflammatory cytokine IL-10
CXCL6 / GCP-2	Activated monocytes	Neutrophil granulocytes	Recruits neutrophils to sites of inflammation
CXCL9 / MIG	IFN-γ stimulated monocytes and endothelial cells	Monocytes, T-cells	Tumorstatic and angiostatic effects; inhibits colony formation of hematopoietic progenitors
CXCL10 / g-IP10	IFN-γ stimulated monocytes and endothelial cells, hepatocytes, keratinocytes	Monocytes, T-cells	Involved in various inflammatory diseases; regulates angiogenic activity in cancer
CXCL12 / SDF-1	Stromal cells of bone marrow	Monocytes, T-Cells	During embryogenesis: regulates migration of hematopoietic cells to bone marrow and development of blood vessels. During adulthood: involved in angiogenesis, carcinogenesis

Table 8: Selection of cytokines (Modrow et al., 2010)(Akdis et al., 2016)(abcam.com/chemokines)

2 Material and Methods

A Pubmed search was conducted with the keywords ‘endometriosis’, ‘cytokines’, ‘diagnosis’, ‘biomarker’, therapy’ and references within identified papers were also reviewed. In addition, relevant textbooks in both English and German language were used.

3 Results

3.1 Pathogenetic role and diagnostic value of cytokines in endometriosis

3.1.1 TNF-alpha (TNF-α)

TNF-α is a cytokine secreted predominantly by activated macrophages and monocytes and it is associated with the physiological cycle of the endometrium. It takes part in proliferation and apoptosis of both endometrial and endometriotic stromal cells by mediating NF-κB and MAP Kinase pathways. Additionally, TNF-α induces IL-8-mediated proliferative effects and promotes inflammatory processes and neovascularization in the endometrium (Iwabe *et al.*, 2000)(Tabibzadeh, 1996)(Harada, Iwabe and Terakawa, 2001). TNF-α can also upregulate expression of ICAM-1 on endometrial cells, a molecule enabling cells to escape immune detection (Rothlein *et al.*, 1988) .

Beside its influence on the proliferation of endometriotic tissue TNF-α has also been associated with endometriosis-related infertility. On the one hand Hill and colleagues reported in the late eighties that this cytokine has a negative effect on spermatozoa motility in vitro (Hill *et al.*, 1987). And apart from that, it was shown by Hill and contributors that TNF-α exerted embryotoxic effects (Hill, Haimovici and Anderson, 1987).

Several studies have reported elevated TNF-α levels in peritoneal fluid as well as serum of endometriosis patients (Mohamed A. Bedaiwy and Falcone, 2004)(Cho *et al.*, 2007)(Xavier *et al.*, 2006). TNF-α levels were shown to be higher in serum

and peritoneal fluid at the early stage of endometriosis than in advanced stages (Pizzo *et al.*, 2002). This is compatible with its proinflammatory effects and its ability to promote acute phase protein production (Witsell and Schook, 1993). TNF-α has also been shown to be associated with an increased number and activity of neutrophils in endometriotic lesions (Rana *et al.*, 1996). Further confirmation of TNF-α role in early endometriosis was brought by Witz, who showed that this cytokine enhanced the binding of endometrial cells to extracellular matrix proteins (Witz, 1999). The reason for this enhanced adhesion was a changed integrin expression by endometrial cells.

Patients that had received a months-long treatment against endometriosis showed a decreased level of TNF-α in their peritoneal fluid (Taketani, Kuo and Mizuno, 1992).

In a three-panel (TNF-α, IL-8 and C-125) biomarker analysis, endometriosis was detected in 89.7% of the cases with a specificity of 71.1% (Mihalyi *et al.*, 2010). Bedaiwy and colleagues published in 2002 that TNF-α could be used as a peritoneal fluid biomarker for endometriosis with a sensitivity of 100% and a specificity of 89% (Bedaiwy *et al.*, 2002). At the same time some other studies found no differences in TNF-α serum concentrations between endometriosis patients and controls (Seeber *et al.*, 2008)(Othman *et al.*, 2008). It looks like that more studies are needed to make a serious statement regarding the use of TNF-α as biomarker.

3.1.2 RANTES (CCL5)

RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted) is a cytokine produced by mesenchymal and epithelial cells and takes part in the inflammatory process of endometriosis by attracting granulocytes, macrophages and NK cells into the peritoneal environment. The latter cells contribute to the progression of endometriotic lesions (Bulun, 2009)(Mohamed A. Bedaiwy and Falcone, 2004). Moreover, it was shown by the working group of Hornung that RANTES is also expressed in endometrial and endometriotic cells (Hornung *et al.*, 1997).

RANTES may also be a contributing factor to endometriosis-associated infertility. In an in vitro study carried out by Isobe et al. in 2002, it was shown that RANTES can attract spermatozoa (Isobe *et al.*, 2002) and therefore high levels of RANTES in endometriosis could interfere with the physiological travel of the sperm to the site of the ovum (Hornung *et al.*, 1997). Moreover, Barbonetti and colleagues found that elevated levels of RANTES could impede the sperms ability to normally interact with the ovum (Barbonetti *et al.*, 2008).

The studies evaluating RANTES levels in endometriosis patients showed contradictory results. Khorram and his team found that the peritoneal fluid levels of RANTES were higher in women with endometriosis and that these levels increased in correlation with the stage of the disease (Khorram *et al.*, 1993). However, Margari and coworkers reported no change in peritoneal fluid levels between patients and controls (Margari *et al.*, 2013). In peripheral blood, one study detected that RANTES levels in patients with endometriosis were elevated compared with controls (Vodolazkaia *et al.*, 2012), while another study found no altered levels (Kalu *et al.*, 2007). Moreover, mRNA levels of the CCR1, one of the receptors that interact with RANTES, were significantly upregulated in endometriosis patients than in disease-free controls (Agic *et al.*, 2007). Wang and team reported that endometrial and endometriotic cells in patients expressed higher levels of RANTES (Wang *et al.*, 2010).

3.1.3 Monocyte chemotactic protein – 1 (MCP-1)

MCP-1 promotes the migration of monocytes out of the peripheral blood into the peritoneal cavity and their transformation to macrophages, which are known to take part in the endometriotic inflammation. Additionally, MCP-1 is also secreted by endometrial cells (Capobianco and Rovere-Querini, 2013).

With regard to MCP-1 concentration in endometriosis patients the findings seem to be incoherent. In their review of 2014, Borreli and colleagues found that five studies reported increased levels, while four others found no altered levels and one even found decreased levels of this cytokine in peritoneal fluid of women with

endometriosis. Likewise, the reviewed studies by Borrelli et al. on peripheral blood levels of MCP-1 were also not coherent. On one hand, five studies reported elevated blood levels in patients with endometriosis and on the other, five studies showed no change in women with the disease versus controls. In contrast, the findings of this team with regard to endometrial tissue was more conclusive, with nearly all reviewed studies pointing to an increased release of MCP-1 by endometrial tissue (Borrelli, Abrão and Mechsner, 2014).
In regard to MCP-1 as a blood biomarker, Akoum and his team showed that MCP-1 had a slight tendency towards identifying the disease with a sensitivity of 65% and a specificity of 61% (Akoum *et al.*, 1995).

3.1.4 Growth-regulated-oncogene-alpha (GRO-α or CXCL1)

GRO-α also known as CXCL1 is expressed by macrophages and epithelial cells. This cytokine takes part in angiogenesis and inflammatory and tumorigenic processes (Bechara *et al.*, 2007).
It may also be involved in endometriosis by attracting neutrophils into the peritoneal fluid and maintaining blood supply to the endometriotic implants (Szamatowicz *et al.*, 2002).

The levels of GRO-α in the peritoneal fluid of women with endometriosis were examined in two studies: one study reported increased levels only in patients with higher disease stages, while the other showed elevated levels in all endometriosis patients. Both concluded that GRO-α may be involved in the formation of endometriosis, by inducing angiogenesis in lesions and stimulating peritoneal fluid neutrophils (Oral *et al.*, 1996)(Szamatowicz *et al.*, 2002).

3.1.5 Thymus and activation regulated chemokine (TARC or CCL17)

TARC is expressed in thymus cells, can be secreted by endometrial gland cells and is involved in the regulation of T-cells (Tsuda *et al.*, 2002)(Vestergaard *et al.*, 2004). In the study of Bellelis et al. significantly reduced levels of TARC were found within the endometriotic lesions among patients with rectosigmoid and

retrocervical endometriosis compared with healthy controls (Bellelis *et al.*, 2013). They concluded that this reduction leads to a lack of inhibition of T-cells. This enables T-cells to proliferate extensively at the cost of other immune cells, resulting in an impaired immune response to endometriotic cells (Bellelis *et al.*, 2013).

3.1.6 Stromal-derived-factor-1 (SDF-1 or CXCL12)

SDF-1 is mainly produced and secreted by the bone marrow, but also by lungs, spleen or liver (Schrader *et al.*, 2002). The production of this cytokine is stimulated by estrogen and inhibited by progesterone or SERMs (Selective Estrogen Receptor Modulator) (Glace *et al.*, 2009). It is involved in cell proliferation, migration and adhesion. SDF-1 also takes part in inflammatory diseases due to its increased expression in inflamed tissues where it acts as a chemotactic factor for lymphocytes (Bleul, 1996). Through its specific receptor, namely CXCR-4, SDF-1 promotes growth of endometrial stromal cells (Ouyang *et al.*, 2018). In a murine model of endometriosis, inhibition of SDF-1 resulted in a reduction of growth and angiogenesis of endometriotic implants (Virani *et al.*, 2013). These properties indicate that SDF-1 may be an important factor in the pathogenesis of endometriosis. This hypothesis is further supported by the fact that several studies found significantly increased concentrations of SDF-1 and its receptor CXCR-4 in endometriotic lesions, peritoneal fluid and tissue of women suffering from endometriosis (Bellelis *et al.*, 2013)(Furuya *et al.*, 2007)(Ouyang *et al.*, 2018).

3.1.7 Monotactin-1 (MTN-1 or CCL16) and Secondary lymphoid-tissue chemokine (SLC or CCL21)

The cytokine MTN-1 is a product of liver, spleen and thymus cells, similar to SLC that is also produced by cells of the thymus and lymph nodes (Youn *et al.*, 1998)(Kozai *et al.*, 2017). Both act as chemoattractants for lymphocytes and monocytes (Youn *et al.*, 1998).

Chand and colleagues suggested that CCL16 as well as CCL21 may play a role in the pathogenesis of endometriosis, since they found that the respective levels of

the cytokines were significantly elevated in endometriotic tissue of women with endometriosis (Chand *et al.*, 2007).

3.1.8 Macrophage migration inhibitory factor (MMIF)

MMIF is a pro-inflammatory cytokine that is secreted by leukocytes after contact with bacterial antigens or endogenous glucocorticoids. It promotes acute immune responses and macrophage activation (Flaster *et al.*, 2007).
According to a study conducted by Mahdian et al. in 2015 the expression of MMIF in endometriotic tissue of women with endometriosis was found to be elevated compared to healthy controls. Furthermore, they point out that blood levels of MMIF were significantly increased in endometriosis patients (Mahdian *et al.*, 2015). Additionally, a study of Zhang and coworkers also published in 2015 showed increased concentrations of MMIF in the endometrium of women with endometriosis. This study also reported that MMIF expression in endometrial tissue of affected patients is associated with estradiol levels and showed a higher sensitivity to estradiol. Therefore they concluded, that MMIF may play a role in the formation of endometriosis (Zhang and Mu, 2015).
Already in 2005 Morin and coworkers evaluated the potential of MMIF as a blood biomarker for endometriosis but could only determine a sensitivity of 65% and a specificity of 66% (Morin *et al.*, 2005).

3.1.9 Interferon-γ-inducible protein-10 (IP-10 or CXCL10)

The cytokine IP-10 is secreted by different cell types such as monocytes, fibroblasts and epithelial cells upon stimulation by Interferon-γ. It is a chemoattractant for monocytes and Th1-cells as well as an inhibitor of neovascularization and shows tumorstatic effects (Neville, Mathiak and Bagasra, 1997).

In 2009 Galleri et al. reported of reduced levels of IP-10 in the peripheral blood of endometriosis patients (Galleri *et al.*, 2009). This observation goes together with the findings of Yoshino et al. in 2003 who found reduced IP-10 levels in the peritoneal fluid of endometriosis patients (Yoshino *et al.*, 2003). However, Galleri

found that the reduction of IP-10 in peritoneal fluid was only detectable in patients with advanced stage endometriosis (Galleri *et al.*, 2009). Decreased production of angio- and tumorstatic IP-10 in women with endometriosis may contribute to further vascularization and growth of endometriotic implants. Thus, the lack of IP-10 may be an important factor in the progression of endometriosis (Kim *et al.*, 2009).

3.1.10 Interferon- γ (IFN-γ)

The cytokine IFN-γ is secreted by NK cells and lymphocytes. It promotes activation of macrophages and has various immunoregulatory functions (Schroder *et al.*, 2004).

In endometriosis, IFN-γ may work together with IL-6 to enhance the expression of cellular adhesion molecules, which are necessary factors in the implantation process of ectopic tissue in the peritoneum (Keenan *et al.*, 1994). Furthermore IFN-γ may also contribute to infertility in women with endometriosis, as it has been associated with embryotoxic effects as it was described by Hill and colleagues already in 1987 (Hill, Haimovici and Anderson, 1987). IFN-γ is also known to induce expression of ICAM-1 on cell surfaces, which is a molecule that allows cells to evade immune detection. The working group of De Placido showed already in the late nineties that ICAM-1 is expressed at higher levels in the serum of endometriosis patients (De Placido *et al.*, 1998).

With regard to peritoneal fluid levels of IFN-γ, results seem to be contradictory. Some studies found no difference between women with endometriosis and controls (Keenan *et al.*, 1994). But other studies reported a decreased IFN-γ level in endometriosis patients (Wu *et al.*, 1998)(Wu and Ho, 2003). These diminished levels may be associated with a dysfunction of T-cells and NK-cells in endometriosis (Wu and Ho, 2003).

According to various studies, it seems to be no difference in IFN-γ blood levels between endometriosis patients and healthy controls (Matalliotakis *et al.*, 2003)(Podgaec *et al.*, 2007)(Hassa *et al.*, 2009). In 2012 Vodolazkaia and her research team examined the potential of IFN-γ as a blood biomarker for endometriosis but only found a sensitivity of 68% and a specificity of 65% (Vodolazkaia *et al.*, 2012).

3.1.11 Granulocyte chemotactic protein 2 (GCP-2 or CXCL6)

GCP-2 is a cytokine that attracts and activates neutrophils (Wuyts *et al.*, 1997). Suzumori et al. reported in 2005 that GCP-2 concentrations in the peritoneal fluid of endometriosis patients was enhanced. Furthermore, GCP-2 levels increased in correlation with disease stage. They suggested that GCP-2 might be a factor in the development of endometriosis, contributing to the vascularization and progression of endometriotic lesions (Suzumori, Zhao and Suzumori, 2005).

3.1.12 Fractalkine (CX3CL1)

Fractalkine has adhesive and migratory functions for immune cells (Bazan *et al.*, 1997). The working group of Shimoya studied fractalkine levels in peritoneal fluid and in peripheral blood of endometriosis patients. They found that cytokine levels were altered only in the peritoneal fluid: compared with controls fractalkine was reduced in endometriosis patients (Shimoya *et al.*, 2005). However, a more recent study carried out by Hou and colleagues in 2016 showed that fractalkine was increased in peritoneal fluid as well as in endometrium and ectopic lesions of women with endometriosis. Furthermore, they reported that fractalkine in endometrial tissue was stimulated by estrogen and was suppressed by progesterone. It was also shown that fractalkine is involved in the invasion and growth of endometrial cells via AKT and p38 pathways and could therefore be a target for novel therapies against endometriosis (Hou *et al.*, 2016). Interestingly, Liu et al. reported recently that fractalkine is involved in endometriosis-associated pain in a murine model of endometriosis. This mechanism could be used in future for pain management approaches as well (Liu *et al.*, 2018).

3.1.13 Epithelial-derived neutrophil-activating protein 78 (ENA-78 or CXCL5)

ENA-78 is a small cytokine that is expressed by peritoneal macrophages and epithelial cells. Its production is induced by IL-1 and TNF-α. It is a chemoattractant

for neutrophils and has angiogenic properties (Walz *et al.*, 1991). Mueller and coworkers showed that ENA-78 is expressed in endometriotic cells. In addition, its levels in the peritoneal fluid of patients with endometriosis were significantly higher than in controls (Mueller, 2003)(Suzumori, Katano and Suzumori, 2004).

3.1.14 Macrophage inflammatory protein-3-beta (MIP-3β or CCL19)

MIP-3β is produced in many organs, but predominantly in the thymus and lymph nodes (Yoshida *et al.*, 1997). It stimulates chemotaxis of different immune cells, including dendritic cell and B-cells (Robbiani *et al.*, 2000).
Laudanski et al. found in 2006 increased MIP-3β levels in the peritoneal fluid of women with endometriosis which might indicate that this cytokine could play a role in the pathogenesis of endometriosis (Laudański, Szamatowicz and Oniszczuk, 2006).

3.1.15 Eosinophil Chemotactic Protein (Eotaxin-1 or CCL11)

Eotaxin-1 is secreted by monocytes and endothelial cells upon stimulation by cytokines. It promotes angiogenesis, chemotaxis of granulocytes and is involved in allergic reactions (Dembic, 2015). According to Hornung et al., Eotaxin-1 is expressed in both endometrial and endometriotic cells. Furthermore, they found increased levels of this cytokine in the peritoneal fluid of patients with advanced stages of endometriosis (Hornung *et al.*, 2000). The working group of Ouyang noted in their study in 2010 that endometriotic cells are stimulated by IL-4 to produce Eotaxin-1. This cytokine seems to contribute to the progression of endometriosis by increasing the blood supply in the disease environment (Ouyang *et al.*, 2010).

3.1.16 Transforming growth factor beta (TGF-ß-1)

TGF-ß-1 is produced by nearly all nucleated cells of the human body. It acts as a suppressor of the immune system by inhibiting pro-inflammatory cytokines and immune cells, such as macrophages, NK-, B-, and T-cells. TGF-ß-1 also

stimulates mesenchymal cells and extracellular matrix proteins. It furthermore takes part in the regulation of apoptosis, angiogenesis, tumorigenesis, and cell differentiation (Gressner and Arndt, 2013).
The working group of Harada suggested in 2001 that TGF-ß-1 may play a role in the pathogenesis of endometriosis by inhibiting NK cells, which normally try to eliminate endometriotic cells in the peritoneum (Harada, Iwabe and Terakawa, 2001). Johnson and coworkers as well as Seoane showed that TGF-ß-1 can promote endometriosis by inhibiting apoptosis in endometrium and endometriotic tissue (Seoane, 2006)(Johnson *et al.*, 2005). Liu et al. demonstrated in 2009 that TGF-ß-1 promoted the implantation of endometrial cells in the peritoneum (Liu *et al.*, 2009) and it was also shown by the research group of Young that it induced angiogenesis in the peritoneal environment in women with endometriosis (Young *et al.*, 2015).
Indeed, Young and colleagues stated in a recent review that “levels of TGF-β are reported to be increased in the peritoneal fluid, serum, ectopic endometrium and peritoneal tissue of women with endometriosis compared to controls” and that “altered TGF-β expression and/or signaling may contribute to the pathophysiology of endometriosis” (Young *et al.*, 2017).
In conclusion, TGF-ß-1 seems to play a crucial role in the pathogenesis of endometriosis.

3.1.17 Vascular endothelial growth factor (VEGF)

VEGF represents a family of growth factors that are produced by nearly all body cells, increasingly under influence of hypoxia and inflammation. VEGF promotes angiogenesis, mitogenesis, and morphogenesis, and it induces chemotaxis of endothelial cells and monocytes (Shibuya, 2013).

VEGF is reported to be increased in peritoneal fluid of endometriosis patients (Kianpour *et al.*, 2013). Otherwise no difference in VEGF levels was found in peripheral blood of endometriosis patients compared with controls (Othman *et al.*, 2008)(Pupo-Nogueira *et al.*, 2007)(Bourlev *et al.*, 2006)(Gagne *et al.*, 2003). Endometriosis patients with severe endometriosis that underwent removal of lesions were reported to have lower VEGF-A concentrations in peripheral blood

than before (Bourlev *et al.*, 2010)(Mohamed, El Behery and Mansour, 2013). But in another study, VEGF levels after androgenic medication were increased compared to them before treatment (Szubert *et al.*, 2014). In spite of these contradictory results, Mohamed and coworkers reported that VEGF may serve very well as a serum biomarker for endometriosis with a “sensitivity of 93.3 %, specificity of 96.7 % and accuracy of 95.0 %” (Mohamed, El Behery and Mansour, 2013).

3.1.18 Interleukin-1 (IL-1)

IL-1 represents a group of cytokines that are produced by activated macrophages and other cells, like endothelial and dendritic cells. It promotes inflammatory and pyrogenic effects, angiogenesis, hematopoietic proliferation, and expression of adhesion molecules in endothelial cells. IL-1 is overall an important regulator of cell growth, differentiation, and cell death (Dembic, 2015).
In endometriosis, IL-1 stimulates vascularization of ectopic tissue (Huang *et al.*, 2013) and it can also induce ICAM-1 on endometrial cells, which shields them from immune detection (Vigano *et al.*, 1998). Keenan and colleagues reported that isolated and cultivated peritoneal macrophages from women with endometriosis produced increased amounts of IL-1 (Keenan *et al.*, 1995). Additionally, increased levels of this cytokine were detected in the peritoneal fluid of endometriosis patients (Sokolov *et al.*, 2005)(Akoum *et al.*, 2008). With regard to peripheral blood samples of endometriosis patients, several studies pointed out that there was no change in IL-1 levels compared to healthy individuals (Bedaiwy *et al.*, 2002)(Szubert *et al.*, 2014).
In 2012 Vodolazkaia et al. reported of the potential of IL-1β as a blood biomarker for endometriosis as they found a rather good sensitivity of 82% but a low specificity of 35%, indicating a low potential in distinguishing endometriosis as a stand-alone diagnostic test (Vodolazkaia *et al.*, 2012).

3.1.19 Interleukin-4

Interleukin-4 is produced by Th2 cells and has anti-inflammatory properties. It downregulates the production of Th1 cells and macrophages, suppressing the pro-inflammatory cytokines that are secreted by them (Dembic, 2015).
Ouyang and coworkers showed that IL-4 contributes to the development of endometriosis by stimulating endometriotic cells to produce angiogenic Eotaxin-1 (Ouyang *et al.*, 2010).
Hsu and colleagues reported mRNA- and protein-levels of IL-4 to be elevated in blood and peritoneal fluid of women suffering from endometriosis. IL-4 levels were reduced after treatment with danazol and laparoscopic surgery (Hsu *et al.*, 1997). Also, Malutan and coworkers found a positive correlation between disease severity and levels of IL-4(Malutan *et al.*, 2016).
However, some studies that evaluated blood levels of IL-4 in endometriosis patients found no change compared with controls (Podgaec *et al.*, 2007)(Hassa *et al.*, 2009).
One study assessed the cytokine's potential as a serum biomarker for endometriosis and found a sensitivity and specificity of 64% and 65%, respectively (Drosdzol-Cop, Skrzypulec-Plinta and Stojko, 2012). IL-4 with its tendency towards diagnosing endometriosis might be useful within a panel of other biomarkers.

3.1.20 Interleukin-6

IL-6 is secreted by macrophages and monocytes. It induces inflammation, acute phase reaction, fever, cell proliferation and also activates B- and T-cells, among a multitude of other effects (Tanaka, Narazaki and Kishimoto, 2014).
Several studies have shown significant increased levels of IL-6 in the peritoneal fluid of women with endometriosis (Wickiewicz *et al.*, 2013)(Kang *et al.*, 2014). Moreover, several papers reported an increase of IL-6 in the serum of endometriosis patients (Othman *et al.*, 2008)(Martinez *et al.*, 2007)(Iwabe *et al.*, 2003). Furthermore, the teams of Akoum and Tsudo demonstrated that endometriotic tissues produce IL-6 in great amounts (Tsudo *et al.*, 2000)(Akoum *et al.*, 1996). In the nineties Tseng et al. found an enhanced secretion of IL-6 in endometrial cells in women with endometriosis, which may indicate a dysfunction of endometrial cells in these women (Tseng *et al.*, 1996). A study of Cheong et al. found that peritoneal fluid levels of IL-6 correlated significantly with the degree of

endometriosis in affected patients (Cheong *et al.*, 2002). Additionally, Bergqvist and colleagues noted that IL-6 levels correlated with the number and size of fresh endometriotic lesions in the peritoneum (Bergqvist *et al.*, 2001). However, Wickiewicz and her working group found that IL-6 could just be used as moderate discrimination factor between moderate and severe forms of endometriosis (Wickiewicz *et al.*, 2013).
In a meta-analysis assessing serum biomarker performance of IL-6 for endometriosis, the cytokine showed a slight tendency to identify the disease with a sensitivity of 63% and a specificity of 69%, indicating it may contribute to a panel of other biomarkers (Dembic, 2015).

3.1.21 Interleukin-8

IL-8 is produced by activated macrophages, monocytes and endothelial cells. Its acts as chemoattractant for monocytes, stimulates endothelial cell and angiogenesis (Dembic, 2015).
A review carried out by Borreli and coworkers in 2014 found 15 studies that reported increased levels of IL-8 in the peritoneal fluid of women with endometriosis. The review found only one study that reported no variation in IL-8 cytokine levels between patients with the disease and controls. The authors explained that this aberrant finding might have been the result of an insufficient number of probands and the fact that they carried co-diseases. Based on published studies the review states that endometrial tissue expresses increased levels of IL-8, being a further evidence for significance of this cytokine in endometriosis. In result it can be concluded, that IL-8 peritoneal and endometrial levels seem to be associated strongly with endometriosis. However, in respect of the blood levels of IL-8, the same review found two contradictory sets of studies. Six studies were found to report increased IL-8 blood levels in endometriosis patients compared to healthy women, but seven other studies did not report any significant change of the cytokine level (Borrelli, Abrão and Mechsner, 2014).
With regard to the role of this cytokine in endometriosis, some studies have found that IL-8 had proliferative effects on endometrium and ectopic endometriotic cells (Li, Luo, *et al.*, 2012)(Arici *et al.*, 1998). Two studies by Garcia-Velasco and coworkers demonstrated that IL-8 concentrations correlated positively with the

tendency of endometrial cells to adhere to extracellular matrix proteins. This adherence process was further shown to be associated with an activation of IL-8 genes (Garcia-Velasco and Arici, 1999a)(Garcia-Velasco and Arici, 1999b). So, IL-8 may play an important role in the implantation mechanism of endometriotic cells in the peritoneal wall and the further growth of these implants.

According to Ohata and coworkers, IL-8 showed a high tendency to identify endometriosis as a serum biomarker for endometriosis with a sensitivity of 71% and a specificity of 81%. The group suggested that further studies on the diagnostic value of this cytokine are needed (Ohata *et al.*, 2008).

3.1.22 Interleukin-10

IL-10 is produced by T-cells and macrophages/monocytes. It is an important immune response regulator that exerts anti-inflammatory effects by suppressing Th1-cells and therefore Th1-secreted inflammatory cytokines (Dembic, 2015).
In the peritoneal fluid of endometriosis patients, IL-10 levels were noted to be higher compared with healthy controls (Wickiewicz *et al.*, 2013) (Punnonen *et al.*, 1996). The working group of Suen assessed in 2014 the peripheral blood levels of IL-10 in endometriosis patients and found it to be increased. Furthermore, they found that suppression of the IL-10 activity in a murine model of endometriosis lead to a reduction in size of endometriotic implants, while supporting IL-10 response by administration of IL-10 resulted in a further development of implants (Suen *et al.*, 2014). The higher levels of this cytokine in endometriosis was suggested to be a reflection of a dysfunctional and suppressed immune function in patients with the disease (Suen *et al.*, 2014).

3.1.23 Interleukin-12

IL-12 is secreted by macrophages, dendritic cells, epithelial cells and endothelial cells. It activates Th1-cells and NK cells, inhibits Th2-cells, and induces the production of IFN-γ (Dembic, 2015). In 2009 Fairbanks et al. reported of higher levels of IL-12 in the peritoneal fluid of women with endometriosis. Furthermore,

the levels of IL-12 correlated positively with the stage of the disease (Fairbanks *et al.*, 2009). In a further study of Itoh and colleagues 2011, IL-12 was administered peritoneally into a mouse model of endometriosis, that led to a significant suppression of endometriotic implants formation (Itoh *et al.*, 2011). Additionally, Mazzeo et al. demonstrated in an in vitro study that IL-12 enhanced the capability of NK cells to detect endometrial cells (Mazzeo *et al.*, 1998). These findings suggest that IL-12 might be a target in a new therapeutical approach on endometriosis by affecting the formation of endometriotic implants.

3.1.24 Interleukin-13

The cytokine IL-13 is secreted by Th2-cells and eosinophils. It is an inhibitor of monocyte activation and pro-inflammatory cytokines (Dembic, 2015).
According to the work of Gallinelli et al. and McLaren et al., the peritoneal fluid of patients with endometriosis shows significantly decreased levels of IL-13 compared with healthy controls (Gallinelli *et al.*, 2004) (McLaren *et al.*, 1997). Reduced IL-13 levels might lead to an increased macrophage activity in endometriosis and thus to an increased development of this disease (McLaren *et al.*, 1997). There were no changes found in serum levels of IL-13 when endometriosis patients were compared with healthy controls (Bedaiwy *et al.*, 2002).

3.1.25 Interleukin-15

The cytokine IL-15 is secreted by a multitude of cell types, including monocytes/macrophages and endometrial cells. It is known to promote pro-inflammatory effects and activates T cells and NK cells (Dunn, Critchley and Kelly, 2002) (Ohteki, 2002).
The working group of Dunn reported in 2002 that endometrial cells in endometriosis patients exhibited a higher production of IL-15 compared with healthy controls. Furthermore they found that ectopic cells in endometriosis patients expressed IL-15 receptors, which seems to be a reason for being influenced by the cytokine (Dunn, Critchley and Kelly, 2002) . Yu et al. assessed

also the role of IL-15 in endometriosis and concluded that this cytokine enhanced implantation and proliferation of endometriotic cells and may prevent NK-cell-mediated immune response from eliminating the implants (Yu *et al.*, 2016). Another aspect, that may link IL-15 to endometriosis is the fact, that it takes part in the hormone-dependent functions of the uterus (Okada *et al.*, 2000).

3.1.26 Interleukin-16

IL-16 is secreted by various cell types, among them monocytes, macrophages and endothelial cells. It activates different immune cells, including macrophages and T cells, and promotes secretion of pro-inflammatory cytokines (Cruikshank, Kornfeld and Center, 2000).
IL-16 levels have been reported to be elevated in the peritoneal fluid of women with endometriosis (Koga *et al.*, 2005). In the peripheral blood however, no difference was found in cytokine levels in endometriosis patients versus healthy controls as it was published by Zang et al. in 2005 (Zhang *et al.*, 2005). According to Azimzadeh and collaborators, IL-16 polymorphisms correlate with the patient's likelihood to develop endometriosis as well as with disease severity (Azimzadeh *et al.*, 2016).

3.1.27 Interleukin-17A

IL-17A is secreted by Th17 cells as well as other cell types such as stromal and endothelial cells. IL-17 A exerts pro-inflammatory effects and stimulates neutrophils, granulocytes and COX-2. In addition, it is associated with autoimmune diseases and tumors (Fossiez *et al.*, 1998) (Fossiez *et al.*, 1996) (Song and Qian, 2013) (Ahn *et al.*, 2015).
IL-17A seems to be associated with endometriosis, since it was shown by Kahn et al. that the cytokine was secreted by endometriotic cells (Ahn *et al.*, 2015). Additionally, they found that an excision of endometriotic tissue resulted in a decline of IL-17A blood levels (Ahn *et al.*, 2015). The study also concluded, that IL-17A plays a role in promoting vascularization and inflammation that is associated with peritoneal endometriotic lesions (Ahn *et al.*, 2015). On the contrary, there were also studies, that could not find any difference in the blood levels of IL-17A

from endometriosis patients compared to controls (Paiva *et al.*, 2014) (Andreoli *et al.*, 2011).

3.1.28 Interleukin-18

IL-18 is a cytokine that is produced by monocytes/macrophages and dendritic cells. It enhances Th1-cells activity, promotes the production of other pro-inflammatory cytokines, induces angiogenesis and stimulates the production of ICAM-1 (Yasuda, Nakanishi and Tsutsui, 2019).
The data that were gathered according to cytokine levels in the peritoneal fluid were contradictive. Some studies reported of elevated concentrations of this cytokine (Arici *et al.*, 2003)(Oku *et al.*, 2004)(Bersinger *et al.*, 2012), whereas another study found decreased levels (Zhang *et al.*, 2004). Moreover, still other researchers found no significant variation between patients and the control group (Glitz *et al.*, 2009) (Fairbanks *et al.*, 2009). These different outcomes could be the result of the different locations and types of endometriotic implants assessed in the studies. Papers that deal with the IL-18 levels in the serum reported about no differences from controls (Glitz *et al.*, 2009)(Zhang, Peng and Meng, 2005)(Oku *et al.*, 2004).

3.1.29 Interleukin-27

IL-27 is secreted by activated macrophages and dendritic cells. The cytokine takes part in antiviral immune response and stimulates Th1 cells (Kempuraj *et al.*, 2004). IL27 was shown to promote endometriotic lesions and the overall progression of endometriosis in a study carried out by Chang and colleagues. They suggested that this finding may advance new treatment possibilities for endometriosis (Chang *et al.*, 2017).

3.1.30 Interleukin-37

IL-37 is produced by macrophages and epithelial cells. It is known to suppress innate immunity and pro-inflammatory cytokines (Nold *et al.*, 2010).

Jiang and colleagues found that endometrial cells and endometriotic implants of patients with endometriosis expressed elevated amounts of IL-37 compared with endometrial cells of healthy controls. Moreover, ectopic cells showed a stronger production of IL-37 as eutopic cells in patients with the disease. According to the researchers, this increase of IL-37 expression might contribute to the inflammatory processes of the disease (Jiang *et al.*, 2016). IL-37 is also known to be upregulated by several other cytokines involved in endometriosis, such as TNF-α, IFN-γ, and IL-1 (Kaabachi *et al.*, 2017).

3.2 Targeting cytokines in endometriosis treatment

Several studies have evaluated the potential of cytokines as target for the medication in the treatment of endometriosis patients.

Targeting TNF-α

A study carried out by Grund et al. in 2008 revealed that the suppression of TNF-α pathways in endometriotic cells resulted in an inhibition of multiple disease progression biomarkers, including epithelial–mesenchymal transition markers, inflammatory cytokines, and mediators of cell adhesion and invasion (Grund *et al.*, 2008).

The administration of the TNF-α blocker onercept or etanercept in a baboon model of endometriosis suppressed the activity and progression of the disease (Barrier *et al.*, 2004) (D'Hooghe *et al.*, 2001). Likewise other research teams that worked with a murine model of endometriosis achieved similar results by administering etanercept (Islimye *et al.*, 2011)(Yildirim *et al.*, 2011). These findings were supported by the results of Falconer et al. who demonstrated that treatment with anti-TNF-α monoclonal antibody C5N causes a significant reduction in endometriotic lesions in baboons with induced endometriosis (Falconer *et al.*, 2006). Furthermore, Onalan and colleagues complete a retrospective study in 2018 that showed that an etanercept injection-therapy resulted in an improved fertility and pregnancy rate among women with endometriosis-related infertility (Önalan, Tohma and Zeyneloğlu, 2018).

Alternatively, just one review summarized the effect of TNF-α blocker on endometriosis-associated pelvic pain and pointed out that no positive results were found (Lu, Song and Shi, 2013).

IL-2 Targeting

The working group of Velasco showed that treating murine models of endometriosis with rIL-2 caused an increasement of lymphocyte levels in the endometriotic lesions and concomitant a decrease in size of these lesions (Velasco *et al.*, 2007). Additionally, Acien and coworkers found that treating endometriomas with rIL-2 intracystic injection aside from drainage and GnRH analogues can decrease disease manifestations and reduce the need for further surgical therapy (Acién *et al.*, 2005).

IL-4 Targeting

Administration of anti-inflammatory cytokine IL-4 in murine models of endometriosis might inhibit proinflammatory cytokines and suppress formation of endometriotic lesions, as reported by Quattrone and colleagues in 2015 (Quattrone *et al.*, 2015). IL-4 may therefore play a therapeutic role in endometriosis patients.

IL-6 Targeting

The research team of Taskin recently assessed the effects of IL-6-targeted treatment on endometriosis in a rat model. They reported that the IL-6 inhibitor tocilizumab led to an overall reduction of endometriotic implants compared with controls (Taskin *et al.*, 2016). Therefore, inhibition of IL-6 could be a pathway that can be targeted in novel medication for endometriosis.

IL-10 Targeting

Suppression of IL-10 activity in a murine model of endometriosis lead to a reduction in size of the endometriotic lesions, while additional administration of IL-10 resulted in a further development of such implants as described by Suen and coworkers in 2014 (Suen *et al.*, 2014). This finding indicates, that inhibiting IL-10 may be a mechanism in future medication.

IL-12 Targeting

In a study carried out by Itoh and his research team, it was shown that IL-12 when administered peritoneally into a mouse model of endometriosis, lead to a significant suppression of endometriotic implant formation (Itoh *et al.*, 2011). Additionally, Mazzeo and colleagues demonstrated in an in vitro study that IL-12 enhances the capability of NK cells to detect endometrial cells (Mazzeo *et al.*, 1998).
These findings suggest that IL-12 might be a target in a new therapeutical approach in endometriosis.

SDF-1 Targeting

A few years back the working group of Virani described that in a murine model of endometriosis inhibition of SDF-1 resulted in the reduction of growth and angiogenesis of endometriotic implants, indicating its potential therapeutic value (Virani *et al.*, 2013).

Interferon alpha-2beta Targeting (IFN-alpha-2b)

In the end of the nineties Ingelmo and coworkers assessed the effects of IFN-alpha-2b administration on a murine model of endometriosis and found that intraperitoneal injected IFN-alpha-2b resulted in a significant reduction in size of endometriotic lesions (Ingelmo, Quereda and Acién, 1999). Furthermore, it was shown a few years later by an in vitro study performed by the research team of Badawy that exposition of endometriotic cells to IFN-alpha-2b resulted in an inhibition of further cell proliferation as long as the levels of the cytokine were maintained (Badawy *et al.*, 2001). These findings suggest that this cytokine might be useful as a therapeutic agent.

4 Summary and Outcome

Cytokines represent a large group of glycoproteins that are involved in cell signaling and chemotaxis. In part, they play a physiological role in the homeostasis of the human body, and apart from that they contribute to inflammatory processes by activating immune cells. They are secreted by a multitude of cells including

lymphocytes, monocytes/macrophages, endometrial and peritoneal cells. In endometriosis, cytokines are reported to take part in the pathogenesis of endometriosis (Harada, Iwabe and Terakawa, 2001).

Despite the precise mechanisms not being understood yet, cytokines seem to play a role in the implantation of ectopic endometrial cells in extra-uterine tissues and the disability of the immune system in detecting and eliminating these foreign cells (Harada, Iwabe and Terakawa, 2001). In addition, cytokines seem to promote inflammation, angiogenesis, and adhesion at the implantation sites as well as pain and infertility in affected patients (Harada, Iwabe and Terakawa, 2001). In particular, TNF-α takes part in proliferation and apoptosis of endometriotic cells and upregulates ICAM-1 on endometrial cells, a molecule enabling cells to escape immune detection (Iwabe *et al.*, 2000)(Rothlein *et al.*, 1988). It is also associated with infertility in endometriosis patients, negatively affecting sperm mobility and exerting embryotoxic effects (Hill *et al.*, 1987)(Hill, Haimovici and Anderson, 1987). RANTES is also associated with endometriosis-related infertility, deflecting sperms from their physiological path to the ovum (Khorram *et al.*, 1993). RANTES and GCP-2 levels correlate positively with disease severity. IFN-γ induces ICAM-1 and enhances production of cellular adhesion molecules, contributing to the implantation process of endometrial cells in the peritoneum (Keenan *et al.*, 1994) (Suzumori, Zhao and Suzumori, 2005)(De Placido *et al.*, 1998). Fractalkine promotes the invasiveness and growth of endometrial cells (Hou *et al.*, 2016) and is associated with pain in endometriosis patients (Liu *et al.*, 2018). TGF-ß-1 and IL-15 promote implantation of refluxed endometrial cells in the peritoneum and prevent their NK-cell-mediated elimination (Yu *et al.*, 2016) (Harada, Iwabe and Terakawa, 2001) (Liu *et al.*, 2009). In addition, TGF-ß-1 inhibits apoptosis in endometriotic tissues (Seoane, 2006). IL-6 and IL-18 induce ICAM-1 on endometrial cells (Vigano *et al.*, 1998) (Yasuda, Nakanishi and Tsutsui, 2019). Additionally, IL-6 levels correlate positively with number and size of fresh endometriotic lesions in the peritoneum of affected women (Bergqvist *et al.*, 2001), as well as with the degree of endometriosis (Cheong *et al.*, 2002). IL-8 promotes proliferation of ectopic endometriotic cells (Arici *et al.*, 1998) (Li, Li, *et al.*, 2012)(Li, Luo, *et al.*, 2012) and increases their tendency to adhere to extracellular matrix proteins, like those of the peritoneum (Garcia-Velasco and Arici, 1999a, 1999b).

IL-12 levels correlate positively with the stage of the disease (Fairbanks *et al.*, 2009) and IL-16 correlates with the patient's likelihood to develop endometriosis as well as with disease severity (Azimzadeh *et al.*, 2016).

Changed concentrations of many cytokines have been detected in patients with endometriosis and their diagnostic potential has been evaluated.
In particular, IL-6, IL-8, MCP-1, RANTES and TNF-α were the most extensively assessed cytokines in studies. Whereby IL-6 levels were shown to be increased in peritoneal fluid, peripheral blood, endometrial and endometriotic cells (Tseng *et al.*, 1996; Othman *et al.*, 2008; Wickiewicz *et al.*, 2013). They further correlated with number and size of endometriotic lesions, and with the overall severity of the disease (Bergqvist *et al.*, 2001). IL-6 was shown to have a diagnostic tendency as serum biomarker for endometriosis with a sensitivity of 63% and a specificity of 69%(Nisenblat *et al.*, 2016).
At the same time IL-8 levels were reported to be significantly elevated in an abundant number of studies assessing peritoneal fluid but also endometrial and endometriotic cells of patients with endometriosis (Ryan *et al.*, 1995). The assessment of IL-8 levels in peripheral blood showed significantly increased levels in some studies, while others found no difference (Carmona *et al.*, 2012) (Fasciani *et al.*, 2001). IL-8 showed a sensitivity of 71% and a specificity of 81% as a serum biomarker for endometriosis, indicating a clear tendency to diagnosing the disease (Ohata *et al.*, 2008).
Although the results on MCP-1 are contrasting with regard to all sample types, this cytokine tends to have a diagnostic potential with a reported serum biomarker sensitivity of 65% and specificity of 61% for diagnosis of endometriosis (Borrelli, Abrão and Mechsner, 2014)(Akoum *et al.*, 1995).
Studies on RANTES levels in peritoneal fluid showed likewise conflicting results (Khorram *et al.*, 1993)(Margari *et al.*, 2013). In peripheral blood and endometrial tissue however, most studies found significantly higher levels of this cytokine among endometriosis patients compared with healthy controls (Vodolazkaia *et al.*, 2012) (Hornung *et al.*, 1997).
With regard to IFN-γ, studies on its blood levels showed no difference between endometriosis cases and controls (Matalliotakis *et al.*, 2003). Studies on peritoneal fluid levels of IFN-γ showed contradictory results, with some studies finding

decreased levels and others finding no differences (Keenan *et al.*, 1994) (Wu *et al.*, 1998).
TNF-α levels were consistently reported to be elevated in peritoneal fluid, and some studies showed them to be also increased in the peripheral blood of endometriosis patients (Mohamed A Bedaiwy and Falcone, 2004) (Cho *et al.*, 2007) (Xavier *et al.*, 2006). TNF-α levels were additionally shown to correlate with the stage of the disease (Pizzo *et al.*, 2002). TNF-α showed high diagnostic potential as a peritoneal fluid biomarker for endometriosis with a sensitivity of 100% and a specificity of 89% (Bedaiwy *et al.*, 2002).

Many other cytokines were reported to have significantly higher levels in peritoneal fluid and/or peripheral blood among women with endometriosis, such as Eotaxin-1 (Hornung *et al.*, 2000), MIP-3β (Laudański, Szamatowicz and Oniszczuk, 2006) , ENA-78 (Mueller, 2003), GCP-2 (Suzumori, Zhao and Suzumori, 2005), Fractalkine (Hou *et al.*, 2016), GRO-alpha (Szamatowicz *et al.*, 2002), SDF1 (Ouyang *et al.*, 2018), MMIF (Mahdian *et al.*, 2015), IL-1 (Sokolov *et al.*, 2005), IL-4 (Malutan *et al.*, 2016), IL-10 (Wickiewicz *et al.*, 2013), IL-12 (Fairbanks *et al.*, 2009), IL-16 (Koga *et al.*, 2005), IL-18 (Arici *et al.*, 2003) and IL-37 (Fan *et al.*, 2018).
Cytokines that were shown to have a higher expression in endometrial and/or endometriotic cells were ENA-78 (Mueller, 2003), Eotaxin-1 (Hornung *et al.*, 2000), IL-37 (Jiang *et al.*, 2016), IL-15 (Dunn, Critchley and Kelly, 2002), Fractalkine (Hou *et al.*, 2016), MMIF (Zhang and Mu, 2015), SDF1 (Ouyang *et al.*, 2018), MTN (Chand *et al.*, 2007), SLC (Chand *et al.*, 2007) and TARC (Bellelis *et al.*, 2013).
Cytokines that showed reduced levels in the peritoneal fluid and/or peripheral blood of endometriosis patients were IL-13 (Gallinelli *et al.*, 2004) and IP-10 (Galleri *et al.*, 2009) (Yoshino *et al.*, 2003) .

Some of the abovementioned cytokines showed conflicting results which can be explained by different study modalities, such as cohort size and quality, sample types and analytical criteria. Furthermore, because cytokines have pleiotropic functions and are involved in different diseases, they may also be influenced by co-morbidities of the study participants.

Initial studies on cytokine-targeted therapies have shown a possible suppression of disease initiation, progression and complications. The TNF-α blockers etanercept and onercept showed good results in animal models of endometriosis by decreasing disease activity (D'Hooghe *et al.*, 2001; Barrier *et al.*, 2004). Administration of Etanercept in women with endometriosis led to an increased fertility (Önalan, Tohma and Zeyneloğlu, 2018). Furthermore, studies on murine models of endometriosis showed that administering rIL-2 (Velasco *et al.*, 2007), IL-6 (Taskin *et al.*, 2016) and IFN-alpha-2b (Ingelmo, Quereda and Acién, 1999) decreased endometriotic lesions and otherwise administering IL-4 (Quattrone *et al.*, 2015) and IL-12 (Itoh *et al.*, 2011) inhibited the formation of the above-mentioned cytokines. Additionally, suppression of IL-10 and SDF-1 led to size reduction of endometriotic lesions (Virani *et al.*, 2013; Suen *et al.*, 2014) . Targeting cytokines and their related pathways could therefore be a future approach for treatment of endometriosis.

In conclusion, cytokines seem to play an important role in the pathogenesis of endometriosis. Although some cytokines, like TNF-α and IL-6, did show good results as biomarkers, a single cytokine may not be enough to precisely diagnose endometriosis in a non-invasive manner. Future studies are needed to assess the most promising cytokines within a group of different types of other useful biomarkers to reach the best results. Furthermore, cytokines may provide a novel target for pharmaceutical application, as initial studies have shown.

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