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Systemic HCG treatment in patients with endometriosis: A new perspective for a painful disease

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Effekt einer systemischen HCG-Therapie auf Patientinnen mit Endometriose: Eine neue Therapieoption

Zusammenfassung. *Hintergrund:* Endometriose ist charakterisiert durch das Vorkommen von endometriumartigem Gewebe außerhalb der Gebärmutter, was zu Dysmenorrhoe, chronischen Unterbauchschmerzen und reduzierter Fertilität führt und eine nachhaltige Verminderung der Lebensqualität besonders während der reproduktiven Jahre verursacht. Die gegenwärtig angewendeten medikamentösen Strategien sind bei meist geringem therapeutischen Effekt oft mit massiven Nebenwirkungen belastet. Interessanterweise kommt es bei schwangeren Patientinnen häufig zu einer deutlichen Besserung von Beschwerden und einer Regression von Endometrioseläsionen. Da es im Verlauf einer Schwangerschaft unter anderem zu einer deutlichen Erhöhung von systemischen HCG-Spiegeln kommt, haben wir erstmals den Einfluss von HCG-Injektionen auf Symptome wie Dysmenorrhoe und Unterbauchschmerzen untersucht.

Patienten und Methodik: 31 therapierefraktäre Patientinnen mit histologisch verifizierter Endometriose erhielten wöchentlich ein bis zwei intramuskuläre Injektionen von 1500 bis 5000 I.E. HCG für einen Zeitraum von drei Monaten bis ein Jahr. Lebensqualität und Schmerzintensität wurden je vor und nach einer zumindest dreimonatigen Therapie mittels QoL Fragebogen und Schmerzintensität mit dem Visual Analog Scale (VAS®)-Instrument gemessen.

Ergebnisse: Unter einer dreimonatigen HCG-Therapie kam es zu einer hochsignifikanten Reduktion von Endometriose-bedingten Schmerzen ($p < 0{,}001$, Wilcoxon-Test) und damit auch zu einer deutlichen Verbesserung von erkrankungsbedingten Parametern wie Schlaflosigkeit ($p < 0{,}001$), Irritabilität ($p < 0.001$), allgemeinem Unwohlsein ($p < 0{,}001$), depressiven Verstimmungen ($p < 0.001$) und Schmerzen bei der Defäkation ($p = 0{,}013$). Obwohl es unter HCG nicht zu einer signifikanten Reduktion von Dysurie kam ($p = 0{,}066$), verbesserten sich Dyspareunie und Dysmenorrhoe ebenfalls eindeutig (jeweils $p < 0{,}001$). Die Gabe von HCG bis zu 12 Monaten (Durchschnitt: 4,42 Monate) führte zu keiner Wirkungsabschwächung.

Schlussfolgerung: HCG-Injektionen führen zu einer signifikanten und klinisch relevanten Reduktion der Schmerzintensität sowie zu einem profunden Anstieg der Lebensqualität in Frauen mit therapierefraktärer Endometriose. Obwohl der bemerkenswerte klinische Effekt von parenteralem HCG nun der Bestätigung durch weitere Studien bedarf, so eröffnen unsere Ergebnisse eine äußerst vielversprechende Perspektive in der Behandlung von Endometriosepatientinnen.

Summary. *Background:* Endometriosis is characterized by the presence of endometrium-like tissue outside the uterus. This condition causes painful periods, chronic pelvic pain, subfertility and a profound reduction in quality of life, especially during women's reproductive years. Currently available medical therapies offer comparatively little therapeutic benefit and are often burdened by considerable side effects. However, since clinical evidence shows that pregnancy leads to alleviation of endometriotic symptoms, we have for the first time examined the effect of human chorionic gonadotrophin (HCG) injections on symptoms such as dysmenorrhea and pelvic pain.

Patients and methods: Thirty-one patients with histologically verified endometriosis refractory to therapy received 1 to 2 intramuscular injections of 1500 to 5000 IU HCG per week for a period of 3–12 months. A QoL questionnaire and the visual analog pain intensity scale (VAS®) were used to evaluate quality of life and pain intensity, respectively, before and after three months of treatment.

Results: Three months of HCG therapy led to a highly significant reduction of endometriosis-related pain ($p < 0.001$, Wilcoxon test) and to improvement of disease-related parameters such as sleeplessness ($p < 0.001$), irritability ($p < 0.001$), overall discomfort ($p < 0.001$), depressive moods ($p < 0.001$) and painful defecation ($p = 0.01$). Dyspareunia and dysmenorrhea also clearly improved (both $p < 0.001$), though HCG did not lead to significant reduction of dysuria ($p = 0.66$). Prolonged therapy with HCG for up to 12 months (mean: 4.42 months) did not lead to reduction of the beneficial effect.

Conclusions: HCG injections lead to significant and clinically relevant reduction in pain intensity and to greatly improved quality of life in women with therapy-refractory endometriosis. The remarkable clinical effect of parenteral HCG in our study will have to be confirmed in additional trials but clearly indicates an extremely promising new perspective in the treatment of endometriosis.

Key words: Endometriosis, HCG, Quality of Life.

Introduction

Endometriosis is one of the most common gynecological diseases and is characterized by endometrium-like tissue outside the endometrial cavity. This condition often results in chronic pelvic pain, dysmenorrhea, subfertility and considerable reduction of quality of life during the reproductive years. A number of treatment strategies have been evaluated over the years; none has been proven universally effective and most are burdened by severe, sometimes unacceptable side effects. Gonadotropin-releasing hormone (GnRH) agonists appear to be most effective in alleviating endometriosis-associated pain but lead to complete gonadal suppression associated with hot flashes, sweats and infertility – one of the main reasons for which women seek medical treatment. Although estrogen add-back may offer some benefit for the clinical complaints of patients, it also reduces the efficacy of GnRH agonists. In addition, the long-term use of GnRH is contraindicated because of the profound loss of bone mineral density associated with its use. Further, there are indications that ablative hormonal treatment of endometriosis may increase the risk of malignant transformation in the endometriotic implants by causing negative selection and increasing the rate of dyskaryosis and loss of heterozygosity [1].

On the other hand, progestins have a better profile of side effects and are more cost effective. However, most studies have found that they are considerably less effective as GnRH agonists, which makes them a treatment option only in less severe forms of endometriosis. Oral contraceptives (OCs) are also generally well tolerated but are only partially effective during treatment and have a high relapse rate after therapy is completed [2]. Studies are currently underway to investigate the therapeutic potential of aromatase inhibitors and selective estrogen receptor modulators (SERMs), but these also function by reducing local concentrations of sex steroids and it is thus unlikely they will be much better than conventional treatment.

Interestingly, pregnancy appears to have a beneficial effect on the course of the disease [3, 4]. The reasons are not entirely clear, but several investigators have demonstrated considerable and sustained reduction of endometriosis-associated pain and regression of endometriotic lesions during pregnancy. Increase of systemic progesterone levels is currently thought to be responsible for this beneficial effect, and we have hypothesized that the effective hormone is indeed human chorionic gonadotrophin (HCG). We have therefore evaluated the effect of HCG on endometriotic symptoms in 31 women with therapy-resistant endometriosis.

Table 1. Patients' characteristics

	Mean	N (%)	Mean duration (months)	min	max
Age	36.7			28	47
BMI	21.97			18.52	29.76
Age at menarche	13.2			12	15
First symptoms at age	17.8			13	25
Cycle length (days)	28			24	30
Regular cycles		17 (55%)			
Previous pregnancy ever		4 (13%)			
Previous deliveries		0 (0%)			
Desire for conception		27 (87%)			
Dysmenorrhea		31 (100%)			
Cycle-dependent pain		31 (100%)			
Previous Danazol		9 (29%)	5.22	3	12
Previous GnRH		21 (68%)	7.64	3	24
Previous therapeutic OC		27 (87%)	4.72	1	10
Previous gestagens		24 (77%)	15.48	3	48
Other therapies					
Acupuncture		1 (3%)	3		
Arimidex		1 (3%)	10		
Previous surgery for endometriosis		29 (94%)		1	5
Previous pain therapy for endometriosis		31 (100%)			
NSAID during last cycle		24 (77%)			
Opiates during last cycle		7 (23%)			
Butylscopolamine during last cycle		7 (23%)			
Use of antidepressants during last cycle		5 (16%)			
Days of work lost during last 3 months		17 (55%)		1	90

Materials and methods

Patients and HCG treatment

All patients signed an informed consent before inclusion in the study. Only women with histologically confirmed, therapy-refractory endometriosis were eligible for treatment in this single-arm prospective trial. All patients underwent a gynecological and medical examination in order to exclude the presence of pregnancy, malignancy, and serious cardiovascular or endocrine disease. Patients received 1500 to 5000 IU HCG i.m. or s.c. 1 to 2 times weekly for 3–12 months (mean duration of HCG treatment 4.42 months).

QoL and pain assessment

Quality of life was assessed with a QoL questionnaire covering endometriosis-related symptoms and overall well-being (Table 2). Symptoms such as chronic pelvic pain, dysmenorrhea and wellbeing were evaluated with the visual analog scale (VAS®), which measures pain across a continuum of values that cannot easily be directly measured (i.e. from none to extreme amount of pain) [5].

Statistical analysis

SPSS software was used for statistical analysis. The Wilcoxon test was used to compare symptom groups before, during and after treatment. A p-value of < 0.05 was considered statistically significant.

Results

Patients' characteristics

Patients in our study cohort had a mean age of 36.7 years (28–47) and had experienced the first endometriosis-related symptoms at a mean age of 13.2 years. BMI ranged between 18.52 and 29.76 (mean 21.97). None of the patients had previously delivered and only four of the 31 (13%) women had undergone a (unsuccessful) pregnancy, although 27 (87%) had expressed their explicit desire to become pregnant. All 31 patients suffered from dysmenorrhea and cycle-dependent lower abdominal pain for which they had previously received pain medication. Twenty-four (77%) had received NSAIDs, seven (23%) had been treated with opiates and seven (23%) with butylscopolamine at least during their last cycle. All women in the study had received at least some endocrine treatment. Nine women (29%) had been treated with a danazol derivate for a mean duration of 5.2 months and 21 (68%) had received GnRH analog for 7.6 months. Twenty-four patients (77%) had previously been exposed to gestagens and 27 (87%) patients had been prescribed OCs. Four patients (55%) used some kind of antidepressant at least during their last cycle, and 17 women reported taking days off work because of endometriosis-related pain during the last three months (Table 1).

Table 2A. Intensity of endometriosis-related symptoms before and after 3 months of HCG (n = 30)

Symptom	pre HCG			3 months of HCG			p-value
	median	min	max	median	min	max	
Pain	8	6	10	4.5	0	7	< 0.001
Sleeplessness	1	0	10	0	0	6	0.001
Irritability	5	1	9	2	0	8	< 0.001
Depressive mood	5	1	10	2	0	7	< 0.001
Household workload	1	0	8	0	0	4	0.001
Dyspareunia	2	0	8	1	0	7	< 0.001
Painful defecation	0	0	8	0	0	7	0.01
Dysuria	0	0	5	0	0	4	0.07
Dysmenorrhea	9	6	10	5	0	8	< 0.001
Overall discomfort	6	2	10	1	0	7	< 0.001

Table 2B. Intensity of endometriosis-related symptoms before and after termination of HCG therapy (n = 31)

Symptom	pre HCG			post HCG			p-value
	median	min	max	median	min	max	
Pain	8	6	10	4	0	8	< 0.001
Sleeplessness	1	0	10	0	0	5	< 0.001
Irritability	5	1	9	2	0	5	< 0.001
Depressive mood	5	1	10	2	0	6	< 0.001
Household workload	1	0	8	0	0	4	0.001
Dyspareunia	2	0	8	0	0	5	< 0.001
Painful defecation	0	0	8	0	0	7	0.04
Dysuria	0	0	5	0	0	4	0.10
Dysmenorrhea	9	6	10	5	0	8	< 0.001
Overall discomfort	6	2	10	2	0	8	< 0.001

Endometriosis-related symptoms before and during systemic HCG therapy

Endometriosis-related symptoms such as pain, sleeplessness and irritability were graded on the VAS© scale from 0 to 10 before treatment, after three months of treatment and immediately after the cessation of therapy. Table 2 shows the reduction of symptom intensities after three months (A) and after cessation of therapy (B). Endometriosis-related pain was reduced from a score of 8 to 4.5 ($p < 0.001$) after three months and was further lowered to 4 ($p < 0.001$) when therapy was continued beyond three months (mean duration 4.2 months). Similarly, pain-related sleeplessness was reduced from a score of 1 to 0 ($p = 0.001$) after three months, an effect that was sustained beyond three months of therapy ($p < 0.001$). Scores for endometriosis-related moodiness and irritability were reduced from 5 before treatment to 2 after three months ($p < 0.001$) and remained at 2 ($p < 0.001$) after longer HCG treatment. The same scoring system was used to assess depressive moods: scores were reduced from 5 pre-treatment to 2 after three months ($p < 0.001$) and remained at a median value of 2 ($p < 0.001$) after longer HCG treatment. Patients also felt that their ability to cope with the daily household workload significantly increased ($p = 0.001$ after 3 months of HCG treatment and $p = 0.001$ when HCG was given for longer). The extent of dysuria did not significantly change under HCG treatment, regardless of the length of treatment ($p = 0.07$ and $p = 0.10$, respectively), but painful defecation, dyspareunia and dysmenorrhea were significantly alleviated after three months ($p = 0.01$, $p < 0.001$, and $p < 0.001$, respectively). Prolongation of systemic HCG beyond three months maintained the symptom improvement ($p = 0.04$, $p < 0.001$, and $p < 0.001$, respectively). Lastly, when overall discomfort was evaluated, patients reported highly significant reduction from a median of 6 on the VAS© score to 1 ($p < 0.001$) after three months of treatment and reduction to a median score of 2 ($p < 0.001$) when the therapy was continued beyond three months (Tables 2A and B, mean values are shown in Fig. 1).

Discussion

Endometriosis is a benign gynecological disease that still presents a great challenge in both diagnosis and treatment despite its prevalence and manifestation exclusively in women's reproductive years. It is estimated that approximately 5.5 million women are affected from endometriosis in the USA alone and that a significant number of female infertilities are caused by the disease. Many women with considerable intraperitoneal manifestations are oligo- or asymptomatic; others experience extremely painful dysmenorrhea or dyspareunia even though only minor endometriotic foci are detectable by diagnostic laparoscopy. The exact pathomechanism of endometriosis is still unknown although several hypotheses exist. Retrograde menstruation has been postulated, which would result in the transport of viable endometrial cells into the peritoneal cavity. This theory might explain the presence of functional peritoneal foci but would not explain the presence of lesions in the CNS or lung. Another theory has suggested systemic spreading of endometriotic cells through the lymphovascular space and through blood vessels. Furthermore, peritoneal mesothelium, which derives from the same celomic wall epithelium as endometrium, has been postulated to undergo metaplastic transformation to endometrial tissue. Such transformation may occur spontaneously or may be facilitated by exposure to chronic irritation from retrograde menstrual fluid. Most studies now agree that endometriosis probably has a multidimensional etiology, including hormonal, hereditary, and immunologic pathophysiologic factors. Sex steroids appear to be pivotal in the development and maintenance of endometriotic le-

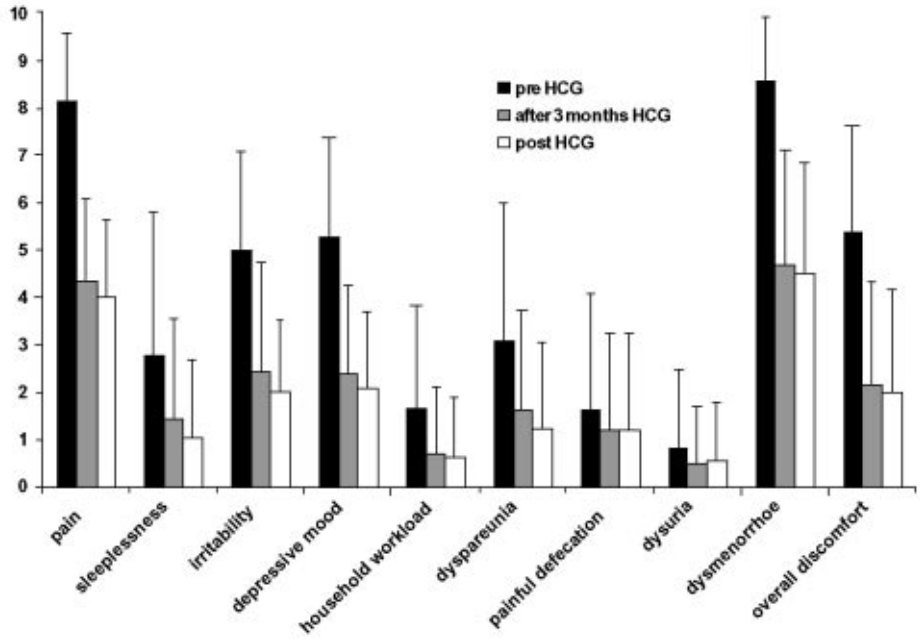

Fig. 1. Mean scores for symptom intensity before therapy (black bars), after 3 months (grey bars) and after the completion (white bars) of systemic HCG therapy (average duration of HCG therapy: 4.4 months)

sions, and recent research has also suggested involvement of the immune system in the pathogenesis of endometriosis. Women with this disorder appear to exhibit increased humoral immune responsiveness and macrophage activation while showing diminished cell-mediated immunity with decreased responsiveness of T cells and natural killer cells. Endometriosis is also characterized by increased expression of pro-inflammatory and pro-invasive cytokines such as interleukin (IL)-1, IL-6, IL-18, Cox-II and TNF-α, and by the release of matrix metalloproteinases (MMPs) probably involved in local invasion and the tissue-lytic processes of endometriotic lesions [6–8].

HCG appears to suppress endometriotic lesions through several pathways: its anti-proliferative and anti-invasive properties are well established and have been proven in a number of in-vitro studies [9, 10]. Recent experiments have also suggested that HCG is involved in the development of immune tolerance and may regulate proapoptotic molecules such as FasL in endometrial cells. Furthermore, HCG-treated endometrial cells increase apoptosis in co-cultured T cells, thus indicating the involvement of paracrine effects [11]. Interestingly, there are several reports linking HCG to an increase of MMPs, especially MMP-9 gene expression, whereas their endogenous inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs), remain essentially unchanged. MMPs are usually considered to be pro-invasive, but MMP-2 and MMP-9 have recently been associated with late stages of wound healing; thus up-regulation of MMPs by HCG might indicate a healing process rather than local invasion [12, 13].

In summary, we have demonstrated that weekly intramuscular injections of 1500 to 5000 IU HCG for a period of three to twelve months lead to a highly significant reduction in pain intensity and to a great improvement in quality of life in women with therapy-refractory endometriosis. Although the prospective study was single-armed and limited by a comparatively small sample size, we nevertheless observed a reproducible and sustained effect. Our finding clearly indicates that HCG is an extremely promising new treatment option, even in patients with hitherto therapy-refractory disease.

We are currently conducting a prospective randomized double-blind trial to confirm our findings and a series of in-vitro experiments to further elucidate the exact mechanism by which HCG exerts its anti-endometriotic effect.

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