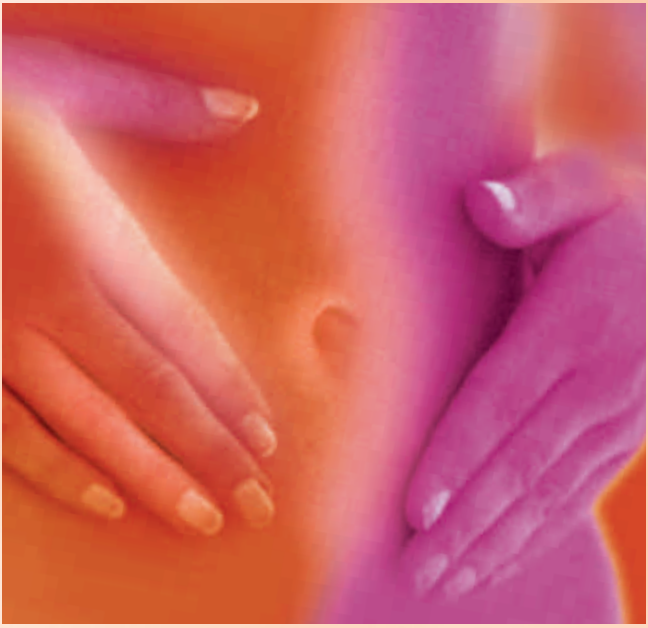
Corticosteroid therapy in inflammatory bowel diseases



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Publisher

FALK FOUNDATION e.V.

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5th edition 2017 (UK)
(Bu80e 10-6/2010)

Corticosteroid therapy in inflammatory bowel diseases

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The discovery of **cortisol** by E. Kendall and O. Wintersteiner in 1937, and its synthesis by T. Reichstein in 1938, made it possible for Ph. S. Hench to use this substance for the first time in 1948 to treat a patient with a rheumatic inflammation of the joint.
Cortisol belongs to a class of hormones known as **corticosteroids** (often simply called cortisone in everyday speech).
Hormones – the word comes from Greek and means "to set in motion" – are the body's own messengers. They are generally released from special glands in response to a stimulus and carried in the blood to their destinations in the body. Hormones then control a number of metabolic processes in their target organs.
The rapid and potent anti-inflammatory effect of cortisol rapidly established the corticosteroids as an effective treatment in acute and chronic inflammation, and also helped its three discoverers to get the Nobel Prize in 1950.

Even then it became clear that the desired activities of the corticosteroids were accompanied by unwanted side effects and only gradually people did learn to avoid these as much as possible, by targeting and limiting the use of corticosteroids.

Treatment with corticosteroids was also a significant advance for patients with **inflammatory bowel disease.** The life-expectancy of these patients was clearly reduced because there was no effective treatment for severe acute exacerbations of the disease. Because of this many young patients died of their disease. The introduction of corticosteroids has almost restored the life-expectancy of patients with Crohn's disease and ulcerative colitis to normal values. The challenge today is to use corticosteroids in such a way that patients are able to optimize their quality of life as a result of their use.

"Cortisone fear" is a widespread problem, resulting from inadequate knowledge among the general public including many patients with inflammatory bowel disease. It is therefore the aim of this patient advice leaflet to present the most important aspects of treatment with corticosteroids in a comprehensible manner.

The natural role and regulation of corticosteroids in the body

The endogenous hormone cortisol and its precursor cortisone are produced in the **adrenal cortex.**

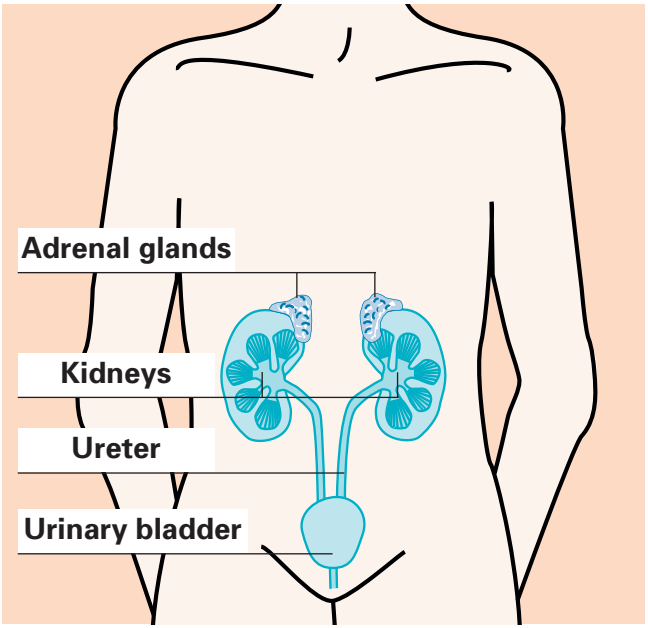

Fig. 1: **Localization of the adrenal glands in relation to the kidneys**

The adrenals, consisting of medulla and cortex, are the organs in the body which act as glands (fig. 1).

Cortisol is essential for the body. The production of cortisol in the adrenal glands is stimulated by a controlling hormone, the **a**drenocorticotropic **h**ormone **(ACTH)** (fig. 2). ACTH is produced in the pituitary gland (hypophysis), a gland which is only the size of a cherry stone and which weighs less than 1 g.

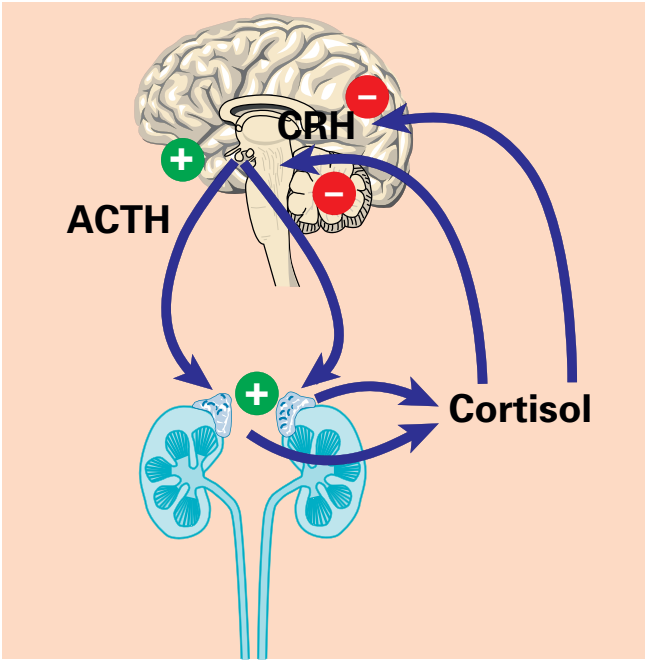

Fig. 2: **The cortisol control system in the hypothalamus, hypophysis and adrenal cortex**

The release of ACTH is controlled by another hormone, the so-called **c**orticotropin **r**eleasing **h**ormone **(CRH).**

CRH is produced in the midbrain in the central nervous system (hypothalamus).

In this complex system, cortisol itself regulates its own release: high concentrations of cortisol inhibit its own release.

This type of control is known as a self-regulating or negative feedback mechanism. Nervous and inflammatory stress factors also have an effect on this regulatory loop.

Cortisol is normally secreted in a **rhythmic manner that depends upon the time of day.** The greatest amounts are released in the early morning with smaller amounts produced during the day and (fig. 3) evening. The adrenal cortex produces about 8–25 mg cortisol per day.

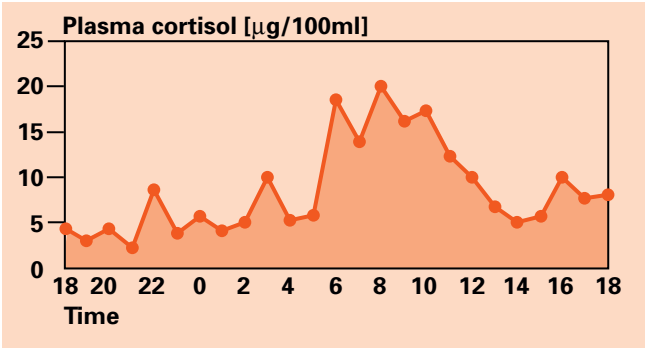

Fig. 3: **Diurnal (related to the time of day) rhythm of blood cortisol levels**

Under severe stress, such as serious illnesses, the body requires more cortisol. The adrenal cortex can produce up to 200–300 mg per day in such situations.

All corticosteroids, including cortisol, act by binding to specific cell **receptors** triggering a variety of metabolic and immune reactions, which are broadly divided into three groups:

1. **Anti-inflammatory effect,** which is important in the treatment of inflammatory bowel disease

2. **General metabolic effect,** which is related to the occurrence of side effects

3. **Effect on fluid balance of mineral/bone metabolism**

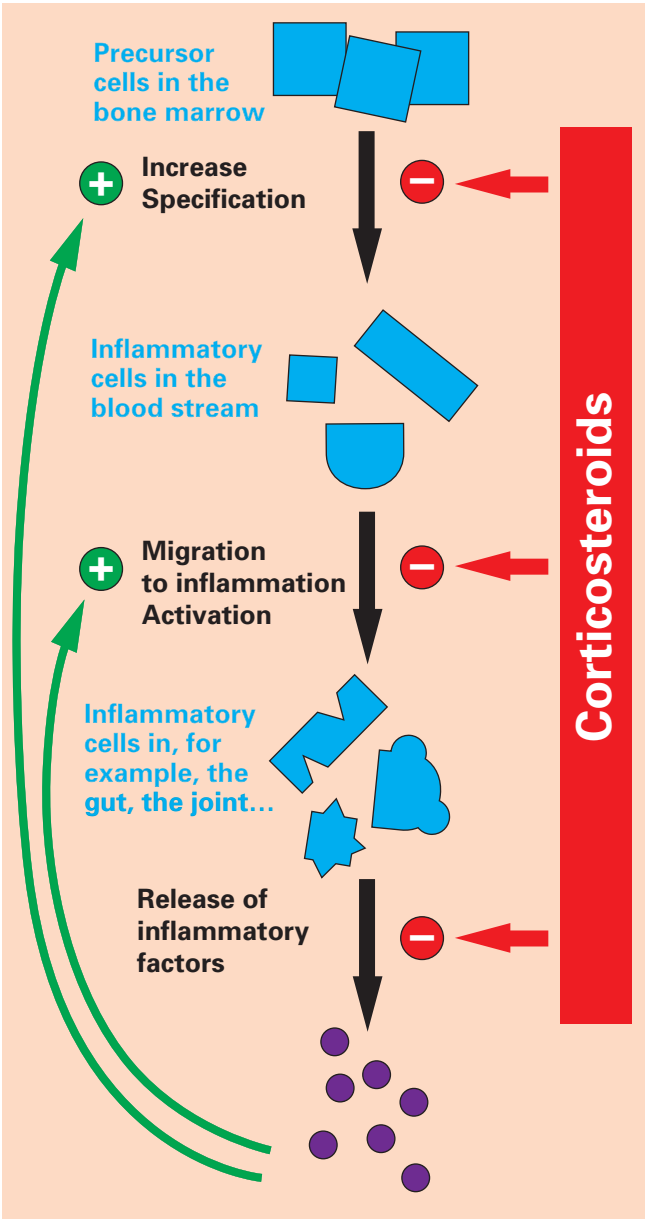

Fig. 4: **Inhibition of inflammation**

Anti-inflammatory properties of corticosteroids

The **anti-inflammatory effect** is due to the fact that corticosteroids inhibit the multiplication (proliferation) and development (differentiation) of inflammatory cells in the bone marrow, the migration of inflammatory cells from the blood into the gut and the activation of these inflammatory cells (fig. 4). Corticosteroids also have a direct effect on all types of inflammatory cells, including the white blood cells (leukocytes). In these, they inhibit the release of inflammatory hormones, such as the cytokines.

The effect of corticosteroids on metabolism

The effect on general metabolism is even more varied. Corticosteroids affect the metabolism of the liver, muscles, fatty tissues, bones and ligaments and many other organs.

The effect of corticosteroids on fluid balance

The effect on fluid balance is due to the cortisol similarity to aldosterone, the hormone which regulates mineral metabolism. Like aldosterone, cortisol increases the retention of sodium and water in the body.

Treatment with corticosteroids

Soon after cortisol was first used in the treatment of inflammatory diseases, attempts were made to increase its efficacy, and at the same time to reduce unwanted side effects, by chemical modifications.

Synthetic corticosteroids to improve efficacy and tolerance

The development of corticosteroids such as prednisolone and 6-methyl prednisolone resulted in corticosteroids with hardly any or with no lasting effect on mineral metabolism whilst at the same time increasing their anti-inflammatory efficacy.

Synthetic corticosteroids have the anti-inflammatory effect 4–5 times greater than the cortisol produced by the human body.

Since all anti-inflammatory and metabolic effects are mediated via the same receptors in the cells it is very difficult to separate the desired effects from the unwanted side effects. In order to achieve progress here, attempts were made to deliver the active substance direct to the site of inflammation, in order to minimize the systemic effects.

Different formulations for the treatment of ulcerative colitis

Initially, formulations for the treatment of ulcerative colitis were designed to achieve high concentrations of corticosteroid in the bowel, i.e. site of inflammation. Relatively high concentrations of corticosteroid can be achieved in the rectum and distal parts of the large bowel through the use of corticosteroid **enemas** (fig. 5).

Some of the corticosteroid enema formulations can be absorbed through the colon mucosa and can lead to unwanted side effects, albeit to a reduced extent. Corticosteroid **foams** are just as effective as the enemas but are preferred by most patients because of their ease of use and better retention.

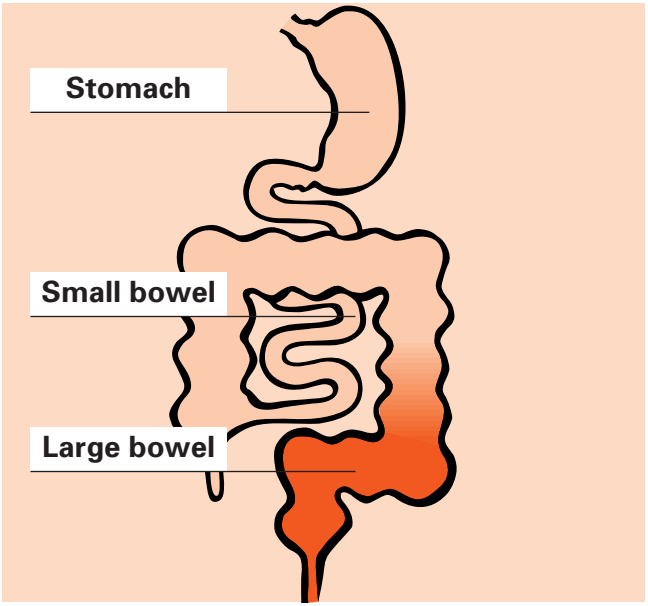

Fig. 5: **Efficacy of corticosteroid enemas and foam preparations in the large bowel**

In some severe or acute cases of the disease, corticosteroids are administered orally or intravenously.

"Topical" corticosteroids

In an effort to preserve the efficacy of the corticosteroids whilst reducing the side effects, so-called **"topical" corticosteroids** have been developed in recent years. Topical means that the anti-inflammatory effect is achieved at the site of inflammation. The principle of "topical" corticosteroids will now be explained using the example of budesonide, which has long been used successfully in asthma therapy, in the treatment of acute Crohn's disease flares with involvement of the ileum and/or the ascending colon and is also approved for rectal therapy in ulcerative colitis.

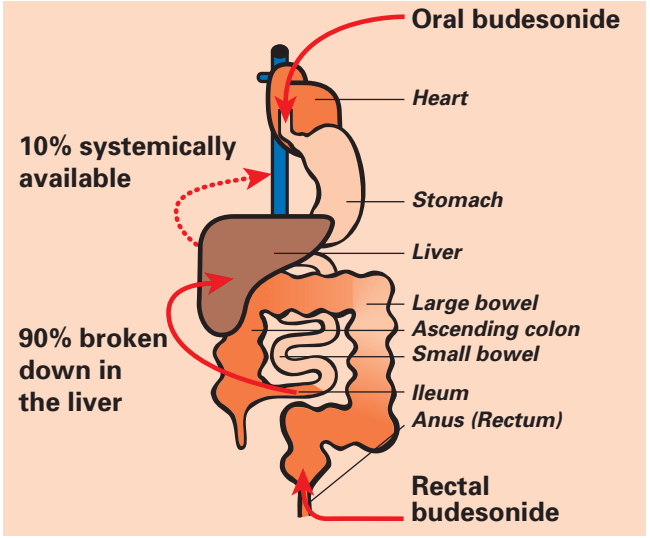

Fig. 6: **The uptake and breakdown of budesonide in the body**

Budesonide is a highly potent corticosteroid. It is rapidly absorbed through the intestinal mucosa when administered orally or rectally after acting at the site of the inflammation, and is carried to the liver. In contrast to the conventional corticosteroids, more than **90%** of the budesonide is broken down during the first passage through the liver so that only a small proportion enters the systemic circulation. This means that fewer side effects are to be expected (fig. 6).

In order for budesonide to arrive at the site of inflammation in the bowel, it is crucial that it must not be absorbed in the upper segments of the small bowel and thus enter the blood stream. A special formulation is used to ensure that the active budenoside is only released at the site of inflammation.

Efficacy in inflammatory bowel diseases

In general corticosteroids are currently the most effective treatment for acute exacerbations of inflammatory bowel diseases (ulcerative colitis and Crohn's disease). Long term treatment with systemic active corticosteroids should, however, be avoided wherever possible.

Ulcerative colitis

Mild to moderate active ulcerative colitis

In mild to moderate active ulcerative colitis, treatment with 5-aminosalicylic acid (mesalazine) is generally sufficient. Occasionally a short course of systemically active corticosteroids (for example 40 mg per day of prednisolone), with a gradual dosage reduction of 10 mg every 5 days and a halt to corticosteroid treatment within 3 weeks, may lead to a more rapid alleviation of the symptoms. As an alternative, a combination therapy consisting of oral formulations and enemas or foam (mesalazine or steroid) preparations may be used. Most patients respond rapidly to this treatment. However frequently, the therapeutic advantages of systemic corticosteroid therapy are usually reduced by the occurrence of side effects.

Left sided ulcerative colitis

In left sided ulcerative colitis, in which only about 75 cm of the large bowel is affected, 5-aminosalicylic acid (mesalazine) enemas or foam formulations have been preferred, and where necessary, corticosteroid foam preparations or enemas can be added. In some cases, it may be necessary to administer a combination of 5-aminosalicylic acid (mesalazine) and corticosteroid rectally, or possibly even a combination of enemas and oral formulations (tablets, granules, capsules).

Severe ulcerative colitis

Severe ulcerative colitis always represents an acute risk to the patient. In these cases it is often unclear whether oral formulations can be effective. On the other hand, enemas and foam preparations are generally unable to be retained for a sufficient period due to severe diarrhoea. Because of this, patient hospitalisation may be needed.

Inactive ulcerative colitis – maintenance of remission

Corticosteroids should not be used for the so-called maintenance of remission (remission = free from symptoms/ absence of active disease), due to possible short and long term side effects. Recommended drugs for maintenance of remission are formulations containing aminosalicylic acid (mesalazine). This therapy also significantly reduces the risk of colon cancer.

Patients who do not tolerate mesalazine may benefit from the probiotic *E. coli Nissle 1917.*

Pouchitis

When patients require complete surgical removal of the colon, a small bowel reservoir (pouch) can be created in many cases, thus permitting regular passage of stool through the rectum.

In some cases, however, the pouch may become the site of chronic inflammation. The standard therapy in such cases consists in the administration of the antibiotic metronidazole. As an alternative, if better tolerated, budesonide can be used as an enema or foam.

Crohn's disease

Mild to moderate active Crohn's disease

Corticosteroids are more effective than 5-aminosalicylic acid in the treatment of mild to moderate Crohn's. Budesonide is recommended as a first choice according to ECCO Guidelines for mild to moderate ileo-caecal Crohn's disease.

Depending upon the disease activity, a variable reduction is recommended.

Weeks	Daily dose of prednisolone
1	60 mg
2	40 mg
3	35 mg
4	30 mg
5	20 mg
6	15 mg
7–14	10 mg
3–6 months	5–10 mg

Tab. 1: **Treatment schedule of active Crohn's disease using prednisolone as an example**

The "topical" corticosteroid budesonide is used as an oral preparation in the treatment of mild to moderate Crohn's disease affecting terminal ileum and caecum. Budesonide is released in the small bowel and the large bowel and acts directly on the inflamed bowel mucosa. After absorption, budesonide will be inactivated in the liver. If the rectum is affected, combination therapy with enemas or foam preparations or systemically effective corticosteroids is recommended.

Severe Crohn's disease

As in ulcerative colitis, patient hospitalisation may be required.

Inactive Crohn's disease – (maintenance of remission)

Corticosteroids are not recommended for maintenance of remission.

Microscopic colitis (collagenous colitis and lymphocytic colitis)

Cases of microscopic colitis can only be diagnosed by microscopic examination of tissue samples from the colon, so it can often take time before the diagnosis is made. Microscopic colitis is characterized by its chronic watery diarrhoea.

Budesonide is the treatment of choice in both forms of microscopic colitis – collagenous colitis and lymphocytic colitis.
It exhibits good efficacy and few side effects. The standard dose is 9 mg of budesonide once a day. With this treatment, the frequency of bowel movements improves in about 90% of patients.

Based on patients' symptoms, the dose of budesonide can be reduced during treatment. Patients, however, must take medication long-term.

Endemic sprue / Coeliac disease

Endemic sprue or coeliac disease is a chronic inflammatory disorder of the small bowel, which is triggered by gluten and gliadin, both proteins are found in grains. Patients experience diarrhoea, abdominal pain and bloating, flatulence, iron and vitamin deficiencies and weight loss.

There is no cure for coeliac disease at present, the only treatment is gluten-free diet.

In the few cases of endemic sprue or coeliac disease that are refractory to therapy, patients have been successfully treated with prednisolone and, more recently, with budesonide.

Tolerability and side effects

Prolonged treatment with systemically acting corticosteroids leads to side effects which frequently force the dose to be reduced or the treatment to be discontinued. The simultaneous appearance of a number of visible side effects of corticosteroids such as weight gain with moon face, buffalo hump, stretch marks (striae), is called **Cushing's syndrome.** Possible side effects of corticosteroids are listed in table 2.

Possible side effects of corticosteroids

- Weight gain, moon face, buffalo hump
- Striae stretch marks on the skin, ecchymoses (small hemorrhages in the skin), acne
- Adrenal cortex atrophy
- High blood pressure
- Osteoporosis (loss of bone density) and aseptic disturbance of blood flow (bone necrosis)
- Minerals disbalance
- Cataract and glaucoma
- Insomnia, psychosis
- Nerve damage
- Inflammation of the muscles, muscle wasting
- Increased susceptibility to infection (immune suppression)
- Growth disturbance (in children)

Tab. 2: **Possible side effects of corticosteroids**

In the following section, some of the possible side effects of corticosteroids will be described in greater detail, together with advice as to what can be done for them.

Osteoporosis is a common and potentially severe complication following prolonged treatment with corticoster-

oids. Spontaneous fractures may occur. Corticosteroids inhibit the formation and stimulate the breakdown of bone by inhibiting the uptake of calcium in the gut and stimulating the release of parathormone (a hormone which promotes the breakdown of bone). If necessary, calcium and vitamin D must be taken. There is evidence that, compared with systemic corticosteroids, budesonide is much better tolerated than systemic corticosteroids also with respect to the risk of osteoporosis.

Corticosteroid-induced bone necrosis is a severe disturbance of blood supply to the bone. Fortunately, it is rare. It predominantly affects the hip joint and manifests itself as pain.

Prolonged treatment with corticosteroids may lead to atrophy of the adrenal glands because the endogenous (naturally produced) cortisol production is suppressed.

It is therefore necessary to avoid abrupt discontinuation of the corticosteroid treatment. The dose tapering has to be gradual so that the adrenal cortex has sufficient time for regeneration and can start secreting cortisol again. Fatigue or faintness are typical symptoms of rapid decrease of corticosteroid dose.

Lens opacities (cataracts) and an increase in the internal pressure of the eye (glaucoma) can also happen when corticosteroids are used for a long time. In order to be able to make the diagnosis at an early stage, regular ophthalmological examinations should be carried out in patients on long-term treatment with corticosteroids.

Suppression of the immune system by corticosteroids also weakens resistance to infection. Because of this, when there are palpable masses in the abdomen, the presence of an abscess (collection of pus) must be excluded before treatment with corticosteroids is started.

Pregnancy and cortisol therapy

There is no increased risk of abortion. The newborn has to be carefully examined by a paediatrician, if high dose of corticosteroids is used during the last period of pregnancy. Untreated or inadequately treated inflammatory bowel disease could be more risky for both mother and baby than an adequate corticosteroid therapy.

Because of the limited experience, there is no general recommendation for the administration of budesonide during pregnancy.

Breast feeding and cortisol therapy

Cortisol may be excreted into breast milk and therefore ingested by the infant and suppression of the cortisol metabolism is possible. This should be carefully checked by a paediatrician. Permanent damage is not expected.

Glossary

5-aminosalicylic acid (5-ASA; mesalazine): active constituent of many medicines for the treatment of inflammatory bowel diseases

Abscess: collection of pus

ACTH: adreno**c**ortico**t**ropic **h**ormone; controlling hormone that stimulates the formation and secretion of corticosteroids. ACTH is produced in the pituitary gland.

Aldosterone: hormone of the adrenal cortex which affects fluid balance

Bone necrosis: severe disturbance of blood supply to the bone with destruction of bone tissue

Budesonide: topically (locally) acting, potent corticosteroid, which can be administered in the form of capsules, granules, rectal foam or enemas

Cataract: opacity of the lens of the eye caused by a variety of factors (congenital or acquired)

Collagenous colitis: type of microscopic colitis characterized by development of a band of collagen fibers over 10 µm in thickness in the wall of the large intestine

Colon: large bowel

Corticosteroids: class of hormones that are released from the adrenal cortex

Cortisol: hormone belonging to the corticosteroid family, regulates a large variety of metabolic processes

CRH: corticotropin **r**eleasing **h**ormone; a controlling hormone which regulates the secretion of ACTH. CRH is produced in the hypothalamus.

Crohn's disease: inflammatory disease of the digestive tract, named after Dr. Burrill B. Crohn, the doctor who first described the disease. Common in the region of the ileum (part of the small bowel) and the colon (large bowel).

Terminal Cushing's syndrome: typical clinical picture of a patient with the increased plasma cortisol level which can occur after a prolonged and high-dose treatment with systemic corticosteroids

Cytokines: hormones which mediate inflammatory reactions (inflammatory mediators)

Differentiation: further development (specialization) of cells

Endemic sprue / Coeliac disease: chronic inflammatory disorder of the small bowel triggered by intolerance to grain proteins

Glaucoma: increased eye blood pressure

Hormone: a messenger substance produced in the body which regulates metabolic processes

Hypothalamus: central nervous region of the mid-brain

Ileum: the lowest section of the small bowel

Immune system: complex system for protecting the body from the substances foreign to the body

Lymphocytic colitis: type of microscopic colitis characterized by increased numbers of lymphocytes in the tissue samples taken from the colon

Microscopic colitis: chronic inflammatory disorder of the colon, which can only be diagnosed by microscopic examination of tissue samples obtained from various sites across the colon

Migration: movement of inflammatory cells from the blood into the bowel

Osteoporosis: loss of bony tissue through increased destruction of bone and/or reduced formation of bone

Parathormone: hormone which is produced in the parathyroid glands and which, among other things, increases the breakdown of bone

Pouchitis: inflammation of the pouch following surgical removal of the colon in ulcerative colitis

Proliferation: multiplication of cells

Psychosis: impaired state of mind

Remission: period of time free from symptoms in a chronic disease

Ulcerative colitis: chronic inflammation of the large bowel

Further information for patients with inflammatory bowel diseases is available in the following Dr Falk Pharma booklets:

– **Ulcerative colitis and Crohn's disease**
  68 pages (S80UK)

– **Nutrition in Inflammatory Bowel Diseases**
  55 pages (S84UK)

– **Crohn's disease and its associated disorders**
  40 pages (S85UK)

These brochures can be ordered **free of charge** from Falk Foundation e.V. or the local Falk partner.

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