Modulatory Effects of Pregnancy on Inflammatory Bowel Disease

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The disease course of autoimmune diseases such as rheumatoid arthritis is altered during pregnancy, and a similar modulatory role of pregnancy on inflammatory bowel disease (IBD) has been proposed. Hormonal, immunological, and microbial changes occurring during normal pregnancy may interact with the pathophysiology of IBD. IBD consists of Crohn's disease and ulcerative colitis, and because of genetic, immunological, and microbial differences between these disease entities, they may react differently during pregnancy and should be described separately. This review will address the pregnancy-induced physiological changes and their potential effect on the disease course of ulcerative colitis and Crohn's disease, with emphasis on the modulation of epithelial barrier function and immune profiles by pregnancy hormones, microbial changes, and microchimerism.

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INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic diseases of the gastrointestinal tract that affects men and women in their reproductive years of life. IBD and IBD therapies can have an impact on fertility, pregnancy outcomes, and fetal/neonatal health. *Vice versa*, the changes in hormones and in the immune system that occur during pregnancy may also influence IBD activity.

There is a clear link between the female reproductive cycle and the gastrointestinal tract, as demonstrated by several studies reporting an increase in gastrointestinal symptoms among women with IBD and irritable bowel syndrome before and during the menstrual period (1,2) and in changes to the menstrual function among women with IBD (3). Physiological changes that occur during the menstrual period include changes in hormones, cytokines, and immune profiles, which may affect gastrointestinal motility, inflammation, and sensitivity (4). Similar changes also occur during pregnancy, and a modulatory role of pregnancy on inflammatory disease behavior has therefore been the topic of research for many years. The most convincing amelioration of (auto)inflammatory disease during pregnancy is observed in rheumatoid arthritis (RA), where symptoms abate during pregnancy, and flares are commonly observed postpartum (5,6). With many of the underlying pathogenic mechanisms (genetics, intestinal microbiome alterations, and immune shifts) overlapping with IBD, resulting in several shared treatment options (7–9), it is not surprising that a disease modulatory role for pregnancy in IBD has also been speculated upon. Nevertheless, conflicting results of the effect of pregnancy in IBD have been observed. One study showed that patients with both CD and UC experienced fewer flares in the 3 years postpartum as compared to their flare rate before pregnancy (10). A 10-year follow-up study confirmed that relapse rates decreased in UC (from 0.34 to 0.18 flares per year) and CD (from 0.76 to 0.12 flares per year) after pregnancy (11). In addition, it appears safe to stop anti–tumor necrosis factor alpha (TNF-α) treatment in pregnant patients with IBD, without increasing the risk of flares (12,13). However, these data are disputed by a study of Pedersen et al. (14), who showed that pregnant women with CD have a similar disease course during and after pregnancy as compared to nonpregnant women with CD. In contrast, women with UC have a higher risk of relapse during pregnancy (relative risk (RR) 2.19) and postpartum (RR 6.22), compared to nonpregnant women with UC. The course of IBD activity during pregnancy is closely related to disease activity preconception (15), with women who conceive during a time of active disease having twice the risk (RR 2.0) of disease flare during pregnancy compared to those who conceive during a time of remission. Although the often-reported medication nonadherence during pregnancy may be a confounding factor (16), disease course during pregnancy appears to be related to the type of IBD, suggesting a true relationship between pregnancy and disease activity.

In this review, we summarize the current knowledge regarding the interaction between reproductive physiology and IBD pathophysiology, and propose explanations for the clinical observations of IBD behavior during the reproductive period. We describe the pathological alterations in barrier function, immunology, and microbiome in IBD and discuss how these factors are modulated during pregnancy. A better understanding of these complex interactions and clinical observations will aid clinicians and researchers in improving the management of IBD during pregnancy, and optimize maternal and neonatal outcomes.

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PATHOGENESIS OF IBD

IBD is a multifactorial disease, in which an altered immune response toward the intestinal microflora results in chronic inflammation of the intestinal tract. In addition to environmental factors (hygiene, smoking, diet, etc.), genetic susceptibility plays an important role in IBD, and large genome-wide association studies have identified more than 200 genetic loci associated with an increased risk of developing IBD (17,18). Interestingly, attempts at identifying common underlying mechanisms based on these loci have uncovered an important role for (innate) immunity and bacterial handling in IBD susceptibility: Many of the identified risk genes can be classified in pathways affecting epithelial barrier function, innate immune cell function, or adaptive immunity. All of these processes are critical at the contact interface between host and bacteria, underscoring the importance of these interactions in IBD development (18).

Epithelial barrier function in IBD

The first obstacle for bacterial invasion is represented by the intestinal epithelial barrier, which, although not traditionally regarded as part of the immune system, is now gaining recognition as part of the first-line innate immune defense. Bacteria are physically separated from the actual barrier cells through the production of a mucous layer and the release of antimicrobial peptides, therein, by goblet cells and Paneth cells, respectively. Disease predisposing genetic variants in mucin genes may contribute to alterations in the mucus layer in patients with IBD (19). With the mucosal layer breached, bacterial components have an increased chance to reach the epithelial cell layer. In response, different immune cells at the mucosa/luminal interface produce inflammatory cytokines, such as interferon gamma (IFN-γ) and TNF-α, which can inhibit antiapoptotic proteins and promote apoptotic processes, resulting in a weakening of the epithelial lining and an increased translocation of pathogens (20). This process, referred to as "leaky gut," is already seen in healthy first-degree relatives of patients and therefore appears to be one of the disease initiating events in patients with IBD. Barrier dysfunction is worsened during active disease, when there is an additional reduction in tight junctions, which regulate the epithelial permeability (21). Thus, the overall weakening of the barrier function in IBD results in an enhanced exposure of the mucosa to bacterial components, which stimulates the attraction of immune cells and perpetuates inflammation.

Epithelial barrier function during pregnancy

Female reproductive hormones fluctuate during the normal menstrual cycle, with estrogen reaching peak levels before ovulation and progesterone reaching peak levels during the luteal phase of the cycle. Fluctuations of these hormones even on estrus scale already appear to affect bowel health. The gut epithelium expresses receptors for both estrogen (estrogen receptor α and β) and progesterone (22), and data in animal models show that paracellular permeability is decreased during the estrogen dominant phase of the cycle as compared to the progesterone dominant phase, consistent with an improved barrier integrity in response to estrogen (23). Gut epithelial cells in female rats are also more resistant to injury and inflammation than in male rats, and application of estrogen to male gut cells abrogates the enhanced inflammatory susceptibility in these male cells (24). Furthermore, progesterone receptor expression is increased in constipated persons, suggesting that even though progesterone does not have a direct effect on barrier integrity (23), it may affect ion and water transport in the gut (25).

With these relatively small systemic fluctuations in hormone levels already impacting epithelial barrier function in an anti-inflammatory and diarrhea-reducing manner, it is tempting to speculate that similar actions on a larger scale take place during pregnancy. Estrogen and progesterone levels increase rapidly during the first trimester, causing some of the nausea women experience. Estrogen peak levels are reached during the third trimester, accounting for the vascularization of the placenta and uterus, supporting the development of the fetus and the development of the milk duct. Interestingly, although low levels of 17 beta-estradiol (17β-EE) decreased paracellular permeability of vascular endothelial cells, high levels of EE increased the permeability, as a result of biphasic modulation of the tight junction molecule occludin (26). Thus, although epithelial barrier function has not been investigated during pregnancy, it is possible that studies performed during estrus are not reflective of a protective role of estrogen during pregnancy. Nevertheless, in irritable bowel syndrome, a link between increased gastrointestinal symptoms at the lowest estrogen levels of the menstrual cycle and reduced complaints during pregnancy is suggestive of a positive effect of pregnancy hormones on intestinal health (27).

IMMUNITY IN IBD

Innate immunity

The immune system represents a complex interplay of different cell types aimed at defending the human body from pathogenic microorganisms. Innate immunity is the first-line defense of the body against infections and includes monocyte/macrophages, granulocytes, and dendritic cells (DCs) (Table 1). These cells, constitutively present in body tissues, act as sentinels of the body by indiscriminate uptake (phagocytosis) and digestion of pathogens. Increased numbers of granulocytes, macrophages, and DCs have been observed in intestinal lesions in IBD. These cells may contribute to exacerbation of disease by releasing damaging reactive oxygen species and increasing local proinflammatory cytokine levels. An inherent alteration in bacterial responses of these cells appears to be present in IBD, which may contribute to the pathogenesis (28–30). For instance, macrophages from patients with IBD show increased proinflammatory and decreased anti-inflammatory cytokines when stimulated with bacteria (31). Epithelial wound healing in colitis models requires the presence of specialized M2 macrophages (32,33), which, in contrast to proinflammatory M1 macrophages, release anti-inflammatory interleukin 10 (IL-10) and contribute to tissue remodeling. In mucosa from patients with IBD, a shift toward M1 macrophages at the expense of M2 macrophages is observed (34), which may contribute to an impaired mucosal healing and prolonged inflammation.

Adaptive immunity

Presentation of pathogenic antigens on the cell surface of DCs and macrophages cells in the context of major histocompatibility complex (MHC) II molecules can subsequently activate cells of the adaptive immune system, in particular CD4+ T-helper cells (Th cells). On antigen stimulation, T cells differentiate into different subsets, depending on the local cytokine milieu. These include Th1, Th2, Th17, and regulatory T cells (Tregs), which each fulfill different functions and produce different cytokines.

Table 1. Changes of the immune system during pregnancy and IBD

	Cell type	Subtype	Function	Changes in IBD	Changes during pregnancy	Conceivable effect of changes during pregnancy on IBD
Epithelial barrier	Goblet cells Paneth cells		Production of a mucous layer Release of antimicrobial peptides	Decrease of mucus layer in IBD Decrease of antimicrobial peptides in IBD	Improved barrier integrity in response to estrogen	Positive effect, mainly due to increase estrogen
Innate immune system; adaptive immune system	Monocytes	Macrophages and dendritic cells (DCs)	Phagocytosis and digestion of pathogens Antigen presentation and activation of the adaptive immune system DCs express IDO1, which induces apoptosis of CD8+ T cells and promotes differentiation of CD4+ T cells to Tregs	Increased in IBD Skewing of macrophages from M2 (important for wound healing) to M1 (inflammatory) phenotype	Decrease from early pregnancy to mid-gestation Skewing toward M2 wound healing macrophages at placental interface Fetal tolerance via Tregs	Positive effects through circulating M2 macrophages and Tregs and their cytokines
	Granulocytes		Phagocytosis and digestion of pathogens Release a number of different effector molecules at site of infection	Increased in IBD	Decrease from early pregnancy to mid-gestation	Decrease during pregnancy may have a positive effect on IBD course
	Natural killer (NK) cells		Secrete cytokines such as IFN-γ and TNF-α, which act on macrophages and DCs Ability to kill tumor cells without any priming or prior activation	Increased in CD	Increase of placental and decidual NK cells	Local effect during pregnancy, so probably no influence on the course of IBD
	Innate lymphoid cells (ILCs)	ILC1 *(IFN-γ, TNF-α)* ILC2 *(IL-4, IL-5, IL-9, IL-13)* ILC3 *(IL-17, IL-22, TNF-α)*	Secrete immunoregulatory cytokines	ILC1 increased in CD ILC2 increased in IBD ILC3 increased in IBD	First trimester: Increase of ILC1 and ILC3	Negative effect on CD, potentially beneficial effect on UC

Table 1. (*continued*)

	Cell type	Subtype	Function	Changes in IBD	Changes during pregnancy	Conceivable effect of changes during pregnancy on IBD
	T cells	T-helper 1 (Th1) *(IL-2, IL-12,* IFN-γ*, TNF-α)* T-helper 2 (Th2) *(IL-4, IL-5, IL-6, IL-9, IL-10, IL-13)* T-helper 17 (Th17) *(IL-17, IL-21, IL-22)* Regulatory T cells (Tregs) *(TGF-β, IL-35, IL-10)*	Cytotoxicity, antitumor and antiviral responses Antibody mediated immunity by stimulating B cells Protect cell surfaces by removing extracellular bacteria Regulate the function of other T-cell subsets and thereby repress inflammatory processes	Increased in CD Increased in UC Increased in UC Increased in IBD	First trimester: Increased in local tissue Second/third trimester: Increase in local tissue Second trimester: Increased	UC more likely to flare during pregnancy CD, not UC, may benefit from the shift to Th2 phenotype Unclear
Hormones	HCG		Mediates early expansion of Tregs Modulates DC responses by inducing IDO1 expression Reduces inflammatory cytokines such as IL-17 while increasing IL-10 levels *In vitro*, hCG is able to stimulate peripheral blood DC subsets to maintain a tolerant phenotype		Increase in first trimester	HCG or its peptides may contribute to the amelioration of inflammatory processes
	Progesterone		Decrease of proinflammatory mediators (i.e., TNF-α, IL-6, IL-1β, NO) Increases IL-10 production by macrophages and monocytes		Increase during pregnancy, with a decrease before labor	Conflicting data
	Estrogen		Decreases inflammatory cytokine production (i.e., TNF-α and IFN-γ) Inhibits NO synthase activity Decreases the recruitment of inflammatory cells		Increase during pregnancy	Conflicting data in animal studies and human studies regarding contraceptive use

Table 1. (*continued*)

	Cell type	Subtype	Function	Changes in IBD	Changes during pregnancy	Conceivable effect of changes during pregnancy on IBD
Microbiome	Bacteria and their metabolites			Reduced diversity of the bacteria present Decrease of anti-inflammatory *Firmicutes* (i.e., *Faecalibacterium prausnitzii*) Increase of proteobacteria and Bacteroidetes phylum members CD show a less stable microbiome and reduced diversity compared to patients with UC	Third trimester: Dysbiosis, resembling a state of low-grade inflammation of the gastrointestinal tract	Worsening of IBD because of increase of dysbiotic changes seen in IBD during pregnancy
Microchimerism	Immune cells, stem cells		Coexistence of two genetically different populations of cells in one individual	Maternal microchimerism is not increased in patients with IBD Fetal microchimerism in IBD pregnancy remains to be investigated	Whole cells cross the placenta from mother to child and vice versa	Fetal microchimerism in IBD pregnancy remains to be investigated, but adverse effects speculated in (auto)immune diseases

CD, Crohn's disease; HCG, human chorionic gonadotropin; IBD, inflammatory bowel disease; INF, interferon gamma; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis.

Distinct cytokine expression differences and T-cell subset activities have been observed between patients with CD and UC (35), and an overactivation of the adaptive immune response with mucosal infiltrating T cells is evident, with the effectivity of targeted therapies against T cells underscoring the importance of this cell compartment in disease activity. Although IFN-γ and IL-17A cytokine expression, representative of Th1 and Th17 cells, respectively, are increased the lamina propria in CD, the Th2 cytokines IL-4, IL-5, and IL-13 are increased in UC (36). Under normal circumstances, Th1 and Th2 cells are in a dynamic equilibrium, with an imbalance resulting in either Th1 or Th2 dominant diseases. Although a gross simplification, CD is now generally regarded as a Th1/Th17 disease, whereas UC is considered as a Th2/Th17 disease.

Tolerance

Of course, with the number of bacteria being equal to the number of human cells in the body (37), it is imperative that the immune system does not respond to all bacteria present. Immune tolerance development is therefore key to a successful symbiosis with our commensal microflora and is largely mediated by Tregs, which suppress T-cell activation through production of cytokines such as IL-10 and transforming growth factor β (38). In addition, on IFN-γ stimulation, DCs express the enzyme indoleamine 2,3,-dioxygenase (IDO1), which converts the essential amino acid tryptophan into kynurenine. This has the dual effect of inducing apoptosis of CD8+ T cells by tryptophan depletion, and skewing CD4+ T cells to Treg differentiation (39,40). Although theoretically it might be expected that regulatory T-cell functions would be decreased in intestinal inflammation, the reverse has been observed: In IBD, both the number of Tregs and their differentiation-inducing agent IDO1 are increased in mucosal IBD biopsies compared to patients with non-IBD (41,42). In part, this seems a (failed) compensatory mechanism, with Tregs from the peripheral blood being recruited to inflamed mucosal area (42). Nevertheless, many experimental models show the benefits of redirecting the Th/Treg balance and suggest that Tregs may be a suitable target for treatment (43). Phenotypic alterations associated with reduced tolerance induction have also been observed for DCs and macrophages in IBD (44,45).

Innate lymphoid cells

In addition to innate myeloid cells, a family of lymphoid-derived cells with innate properties exists, which includes natural killer (NK) cells and a relatively recently identified subset of cells called innate lymphoid cells (ILCs) (46) (Table 1). These cells are enriched at the intestinal mucosa, but unlike "real" lymphocytes, they do not require antigen recognition in MHC II context, but rather rely on myeloid-derived cytokines and natural cytotoxicity receptors for their activation (47). Increased numbers of IL-17 and IFN-γ producing NK cells and ILCs have been observed in mucosal biopsies from patients with CD (48,49), but not from patients with UC (50). Although several experimental models have now highlighted the importance of ILCs for IBD pathology (reviewed in (51)), and NK cell populations are a target for treatments such as 6-mercaptopurine and azathioprine (48,52), cytokine disturbances in IBD have traditionally been linked to a skewing in adaptive immune responses, in particular those represented by Th-cell subsets.

Immunity during pregnancy

Many excellent reviews have already been written on the immunological changes taking place during pregnancy (53–56), the main findings of which are summarized here.

During pregnancy, an MHC mismatched fetus is present in the mother, which, despite the presence of a placental barrier, still affects the maternal immune system. Thus, induction of tolerance against paternal antigens appears to lay at the heart of immunological changes in successful pregnancies. Immune cells infiltrate the placenta during pregnancy, around 70% of which consists of NK cells. Unlike peripheral NK cells, placental NK cells are not cytotoxic, but help decidualization, angiogenesis, immune tolerance, and fetal development by producing growth factors (57,58). Decidual NK cells may possess both immune-activating and regulatory properties (59), and although their presence is beneficial during early pregnancy, their persistence or failure to switch to a different phenotype in later pregnancy is associated with adverse pregnancy outcomes (60,61).

The remainder of placental immune cells consists mostly of macrophages and T cells, including Tregs. Macrophages in the decidua show a distinct M2 phenotype and are a major source of placental anti-inflammatory IL-10 and show reduced T cell-activating properties compared to their peripheral blood counterparts (62). They (as well as DCs and trophoblasts) are an important source of the soluble IDO1 enzyme, which contributes to the generation of Tregs and establishment of fetal tolerance (63). It has been postulated that a shift from inflammatory Th1 to more permissive Th2 cytokine profiles is required for a successful pregnancy (64,65). IL-25, an IL-17 family member expressed by decidual T-cells, NK cells, Tregs, and macrophages, stimulates the production of IL-4 and IL-10 in decidual T cells, thereby contributing to a Th2 environment in first-term placentas (66). Furthermore, human term placentas show increased levels of Th2 cytokines compared to preterm placentas (67,68). However, it is increasingly accepted that a healthy pregnancy depends on the maternal immune system to adapt to the different stages of pregnancy, and that proinflammatory processes are also required for the tissue remodeling, which is essential for decidua formation and labor induction (53). For instance, despite the presence of IL-10, the first trimester of pregnancy is also characterized by the presence of a proinflammatory Th1 immune profile for the successful implantation of the blastocyst, and IL-6, IL-8, and TNF-α are present at the implantation site (55). The source of these cytokines may be Th1 cells (69), although ILC1 and specialized ILC3 cells have also been observed in first-term placentas (70). Cell subsets shift during pregnancy, with the presence of macrophages declining from early to mid gestation, whereas T-cell frequencies increase during this time interval (71). Term labor and delivery appears to require low-level, well-controlled inflammatory processes (72). Correspondingly, placental IL-10 levels decrease toward labor (73), and rat models indicate an increase IL-6, TNF-α, and IL-1β in term placentas (74).

In toto, the current general consensus suggests that implantation requires a Th1 response, followed by a shift toward a Th2 phenotype for the main duration of pregnancy and again a Th1 milieu toward partition (75). It should be noted, however, that much of the data come from animal studies, which may not necessarily reflect the human situation as in contrast to human placentas, T cells represent a rare population in mouse placentas (76).

Systemic immunological effects of pregnancy on IBD?

Differences in disease behavior between CD and UC during pregnancy and peripartum may potentially be explained by intrinsic differences in the immune pathways that lead to each disease. As seen above, pregnancy is associated with immunological changes at the fetal/maternal interface, with a predominantly Th2/tolerogenic phenotype. Thus, it is tempting to speculate that a Th2 shift during pregnancy ameliorates disease in those patients in whom Th1 responses dominate (such as CD), while aggravating disease in Th2 dominant patients (mainly UC). Nevertheless, the maternal peripheral immune system is still capable of mounting a robust immune response to pathogenic antigens (77), and the question therefore remains to what extent placental immunological changes can affect immunological processes at distant body sites.

Levels of Th1 and Th2 patterns *in utero* generally appear to be mirrored by ratios in peripheral blood (53), although most data are derived from studies comparing pregnancy outcomes, and hence blood is usually obtained at only one timepoint, often postpartum. There are conflicting data on modulation of serum cytokine levels in healthy pregnant women, with some studies reporting a significant decrease of proinflammatory Th1 cytokines (e.g., IL-8, IL-12, IFN-γ, and TNF-α) from first to third trimester in healthy pregnant women (78), and others showing no difference or even an increase (79,80). For Th2 cytokines, even less is known, with one study reporting a stable level of IL-4 and IL-5 during pregnancy (81). Thus, it is unclear to what extent pregnancy induces peripheral cytokine changes, which may influence inflammatory diseases. However, ample evidence suggests that peripheral blood cell subsets at least are altered in normal pregnancy. For instance, stimulated peripheral blood mononuclear cells from pregnant women produce less Th1 and Th2 cytokines compared to healthy controls, in particular during second trimester, whereas levels increased postpartum, suggesting that systemic alterations in cell sensitivity exist during pregnancy, which may contribute to decreased (auto)immunity during pregnancy and increased flaring thereof, afterward (82). The peripheral blood percentage of Tregs also peaks during the second trimester of pregnancy, and *in vitro*, these Tregs are capable of reducing T-cell activation in response to DCs (83). Because development of Tregs during pregnancy appears to be related to the presence of fetal alloantigens rather than pregnancy hormones (84) and the Treg recognition receptor repertoire differs per organ (85), it is uncertain to what extent pregnancy-induced circulating Tregs would be useful at the inflamed mucosa. Nevertheless, much is unclear regarding mucosal Treg antigen recognition (86), and the fact that peripheral blood Treg levels drop during inflammation suggest that general recruitment of Tregs to inflammatory sites occurs (42). Their presence there may potentially contribute to modulation of inflammatory processes through production of inhibitory cytokines or suppression of DC maturation.

Similar to Tregs, NK cells present in preimplantation endometrium show a different receptor repertoire compared to peripheral blood NK cells in the same women (87). However, it has also been reported that in the first trimester of pregnancy, progesterone-dependent expression of the receptor T cell immunoglobulin and mucin-domain–containing-3 on peripheral blood NK cell confers immunosuppressive properties (88), and it is conceivable that these cells also reach the intestinal mucosa where they may modulate disease activity.

Systemic effects of pregnancy hormones

The most important early immune modulator in pregnancy is now acknowledged to be human chorionic gonadotropin (hCG), which mediates early expansion of regulatory T cells (Tregs), modulates DC responses by inducing IDO1 expression, and reduces inflammatory cytokines such as IL-17 while increasing IL-10 levels (89). Importantly, many of these effects occur in peripheral blood from nonpregnant patients receiving hCG for their in vitro fertilization treatment. *In vitro*, hCG is able to stimulate peripheral blood DC subsets to maintain a tolerant phenotype (90). Several cleaved or "nicked" forms of hCG exist *in vivo*, and studies have shown that such hCG peptides show anti-inflammatory properties in a host of mouse models, including lipopolysaccharides-induced septic shock, polymicrobial sepsis, hemorrhagic shock, and diabetes (91–96). Administration of hCG peptides also inhibited neutrophil recruitment and inflammatory markers such as IL-6 and TNF-α (89,96,97). The same authors also showed that human graft vs host disease at the skin was successfully treated with hCG, which corresponded with increased IDO1 expression in peripheral mononuclear cells, and also IL-10 serum levels and Treg upregulation (98). With hCG administration being able to prevent autoimmune diabetes in mice by downregulating Th1 responses (99), the use of hCG to control the autoimmune processes in RA and Sjogren's disease has been suggested (100), and it is tempting to speculate that hCG may also positively affect IBD.

The high amount of progesterone throughout pregnancy not only results in the laxity of the ligaments and joints, but is also thought to suppress the maternal immunologic response to fetal antigens and allows implantation in the endometrium. Progesterone reduces proinflammatory mediators (i.e., TNF-α, IL-6, IL-1β, and nitric oxide (NO)) and increases IL-10 production by macrophages and monocytes (101). Application of progesterone in a temporomandibular joint inflammation model of ovariectomized rats reduced synovial inflammation and levels of TNF-α and IL-1β (102). In a rat colitis model, progesterone ameliorated disease activity through reduction of TNF-α levels in colon and blood (103). Nevertheless, conflicting data have also been reported. In a chemically induced model of colitis 2,4,6-trinitrobenzene sulfonic acid, the progesterone dominant luteal phase of the menstrual cycle was associated with increased severity of colitis and treatment of ovariectomized animals with progesterone similarly increased disease severity, whereas estrogen decreased colitis (104). Indeed, anti-inflammatory properties have often been ascribed to estrogen, because it decreases inflammatory cytokine production (i.e., TNF-α and IFN-γ) inhibits NO synthase activity and decreases the recruitment of inflammatory cells (105,106). However, animal studies of IBD and the effect of estrogen also show inconsistent findings. Improvement of stool scores in human leukocyte antigen-B27 transgenic rats with chronic diarrhea was noted after treatment with 17α-ethynyl-17β-EE (107). Similarly, estrogen reduced TNF-α, IL-1β, and IL-6 levels, as well as inflammation in diverse rat models of colitis (108). Verdu et al. (109) found that a supraphysiological dose of 17β-EE has an anti-inflammatory effect in a dextran sodium sulfate murine model for colitis but a proinflammatory effect in the dinitrobenzene sulfonic acid colitis model. Clinical human studies of IBD and sex hormones focus mainly on postmenopausal women and/or oral contraception use. Kane et al. (110) described a protective effect of estrogen on the bowel in women with IBD, whereas Khalili et al. (111) showed that postmenopausal women who use oral contraceptives had a higher risk of developing UC, but not CD. A meta-analysis of Cornish et al. (112) demonstrated that with time of exposure to oral contraceptives, the risk of developing CD was increased, and when contraceptives were stopped, the risk decreased again to that of the normal population.

It is clear that there is conflicting data on IBD and levels of sex hormones and that it is difficult to translate these clinical studies to the situation in a pregnant patient with IBD. Different immune cells may react in an opposite manner to different concentrations of estrogen and progesterone, and expression patterns of receptors of these hormones may vary under inflammatory conditions, precluding robust predictions on the overall effect of progesterone and estrogen on autoimmune disease.

MICROBIOME IN IBD AND PREGNANCY

As mentioned before, IBD is thought to arise in consequence of an altered immune response toward intestinal bacteria. We now know that the microbiome of patients with IBD is substantially altered as compared to healthy controls, and that inflamed regions show further microbial deregulation as compared to noninflamed regions (113–115). This so-called dysbiosis includes a reduced diversity of the bacteria present, in particular in patients with CD, with a noted decrease of anti-inflammatory *Firmicutes* (i.e., *Faecalibacterium prausnitzii*) and an increase of proteobacteria and Bacteroidetes phylum members (i.e., *Bacteroides fragilis*) (116–119). The host–microbiome interaction is reciprocal, and it is as yet unclear whether dysbiosis in IBD presents the chicken or the egg in the etiology of disease. Nevertheless, the general consensus now favors a causative role for the microbiome in disease initiation, because animal models indicate that bacterial presence is required for colitis development and that colitis may be conferred by transplantation of inflammation-associated feces (120).

Pregnancy is also accompanied by intestinal microbial changes. These changes induce a metabolic state that may be beneficial during pregnancy, as concluded by Koren et al. (121). They described that, in the first trimester of pregnancy, the gut microbiota is similar in many aspects to that of healthy nonpregnant controls. However, in the third trimester, a dysbiosis was observed, resembling a state of low-grade inflammation of the gastrointestinal tract. This dysbiosis was accounted for by the presence of Proteobacteria and Actinobacteria and was not related to body mass index (before pregnancy), antibiotic use, diet, or the presence of gestational diabetes. The overall diversity of the bacteria was also reduced at T3. These data would suggest that microbial changes that occur during normal pregnancy fortify dysbiotic changes seen in IBD, and would aggravate disease activity. Interestingly, patients with CD show a less stable microbiome and reduced diversity compared to patients with UC (122), and it is conceivable that further alterations during pregnancy therefore have less of an effect on CD disease activity as compared to UC. Of note, there are several studies which show that diet shapes the microbiome, and in particular, western diets are associated with IBD (123,124). Because it is commonly appreciated that women change their diet during pregnancy, it is important to take this into account in future studies.

It is clear that while microbial changes during pregnancy and the host defense mechanisms are both changed during pregnancy and IBD, the interactions are complex, reciprocal, and double edged, hampering interpretations of the observed changes.

MICROCHIMERISM AND α-FETOPROTEIN

The placental exchange of maternal and fetal gases, nutrients, metabolic waste products, and antibodies is well described. However, in addition to these small molecules, it is also possible for whole cells to cross the placenta from mother to child and *vice versa*. Such coexistence of 2 genetically different populations of cells in one individual is termed (micro)chimerism. Cellular transport is bidirectional (125,126), with maternal cells detected in 24%–42% of fetal-derived samples, and fetal cells were detected in 26%–51% of mothers (127,128). Fetal cells, which can be detected as early as 7 weeks gestation, are known to persist for some time after delivery (129). In fact, microchimerism has been observed in mothers up to 38 years after pregnancy, and in offspring well into adult life (130,131). In addition to fetal mature T-cells, CD34+ progenitor cells enter the maternal bloodstream during pregnancy, which retain their multilineage potential and can become adult hematopoietic cells of all linages and epithelial cells (131,132). With the potential for these cells to assert effector functions and affect the maternal immune system, the functional immunological consequences of these microchimers in health and disease are gaining interest (133,134). Male fetal cell-derived T-cell clones isolated from parous women show proliferation and IL-4 production in response to *ex vivo* stimulation with maternal T cells and MHC antigens, and this effect was higher in patients with systemic sclerosis, suggesting that these offspring T cells show a Th2 profile and could play a pathogenic role in immune disease (135). Interestingly, increased microchimerism was observed in peripheral blood mononuclear cells from patients with the autoimmune disease scleroderma, which has a peak incidence in women after childbearing years, again suggesting that such microchimerism may contribute in autoimmune disease (131). However, patients with either Grave's disease or Hashimoto's thyroiditis, two other autoimmune diseases associated with pregnancy, have reduced microchimerism as compared to healthy controls (136). Furthermore, microchimerism has been investigated in systemic lupus erythematosus (SLE), Sjogren's syndrome, multiple sclerosis, and RA, and may be either protective or harmful (133). In RA, where there is a clear beneficial effect of pregnancy on disease course, it had been suggested that accumulation of fetal T cells, which appear around gestational week 13, may dampen the maternal immune response, and that this effect weakens over time, because of senescence of these cells (137). The presence of fetal cells in maternal tissues correlates to the presence of maternal Tregs, which may account for some of the dampening of inflammatory disease during pregnancy (134). Although the exact effect of microchimerism on (auto)immune disease is as yet unclear, it is tempting to speculate that it may also play a role in IBD and affect disease course during pregnancy. Thus far, only maternal microchimerism has been studied in IBD, which did not appear to be increased in patients with IBD (138,139). Fetal microchimerism in IBD pregnancy remains to be investigated.

Another potential fetal source contributing to maternal (auto) immune response is α-fetoprotein (AFP), a protein produced by the yolk sac and fetal liver, which can be detected in the maternal serum from week 14 of pregnancy onward. AFP was shown to bind to autoantibodies produced in patients with the autoimmune disorder myasthenia gravis (MG), and it was thus speculated that circulating levels of AFP in the second and third trimester of pregnancy could induce clinical remission in patients with myasthenia gravis during these times (140). The immunomodulatory effects of AFP extend beyond antibody binding (141). Studies indicate that AFP ameliorates a mouse model of multiple sclerosis (MS), through, among others, inhibition of Th1 cytokine production (142). It has been speculated that AFP may be used for the treatment of myasthenia gravis, MS, autoimmune uveitis, and psoriasis (143). Thus far, however, the potential role of AFP in IBD remains unexplored.

MODULATION OF IBD RESPONSE TO MEDICATION THROUGH PREGNANCY

Disease activity in women with IBD may also be modulated by pharmacokinetic changes induced by pregnancy and through interaction of IBD medication with the placenta, which may modulate the clinical effectivity of these drugs. However, although drugs such as the thiopurine 6-thioguanine nucleotide and 5-aminosalicylic acid are known to cross the placenta, this does not seem to influence therapeutic levels in the mothers (144). Less is known about the effects on patient and child outcomes of biologicals, the most recent IBD medications. The earliest of these are the anti-TNF-α treatments (infliximab, adalimumab, golimumab, and certolizumab pegol), with vedolizumab (α4β7 integrin blocker) and ustekinumab (IL-12/IL-23 blocker) following suit. From week 20 onward, maternal immunoglobulins (Igs) are transported across the placental barrier, to provide immunoprotection to the fetus (145). Transport of Igs is mediated by the neonatal fragment crystallizable (Fc) receptor (FcRn), which binds to the Fc region present in all antibodies, including therapeutic monoclonal antibodies. Certolizumab pegol does not undergo this FcRn-mediated transfer across the placenta, because it lacks an IgG Fc region and therefore does not bind FcRn. Owing to the passive diffusion across the placenta, the levels of certolizumab pegol reaching the fetus are probably much lower when compared to infliximab and adalimumab (146). We and others have previously shown that infliximab and adalimumab levels in cord blood exceed levels present in serum from mothers treated with these medications (147,148), suggesting that active transport of these antibodies over the placental barrier may decrease bioavailability of the antibodies in the mother. As serum drug levels of these therapeutic antibodies correspond to clinical outcomes for patients with IBD, modulation of these levels through placental transport could potentially result in disease relapse (149,150). Thus far, however, maternal infliximab levels during pregnancy were shown to be increased, whereas adalimumab levels remained stable. Nevertheless, pharmacokinetic changes of these therapeutic antibodies on pregnancy have only been studied in a small cohort of patients, and larger studies are needed (151).

SUMMARY

The observation that the disease course of several (auto)immune diseases are altered during pregnancy suggests that there is an interaction between physiological changes taking place during pregnancy and pathophysiology of these diseases (Figure 1). For IBD, this relationship appears more apparent for UC than CD, which may be due to the fact that CD and UC have differential underlying genetic susceptibilities, immune profiles, and microbial changes. Genetic variants affecting cellular innate immunity are associated more with CD, whereas UC-specific single nucleotide polymorphisms affect epithelial barrier function genes (152). Furthermore, patients with CD show a more Th1 dominant

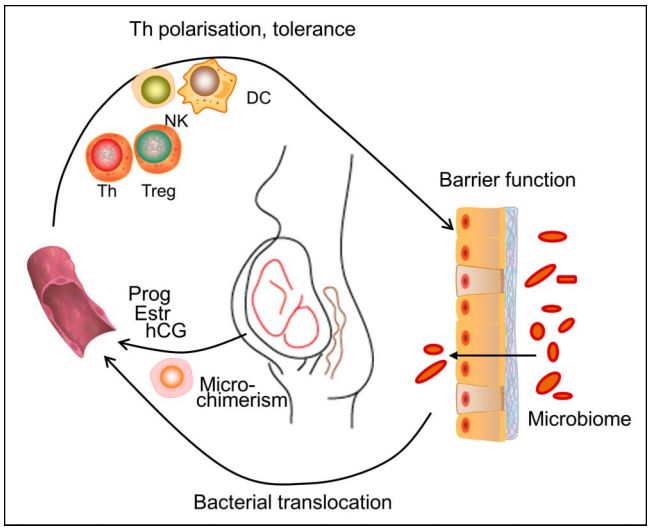

Figure 1. Interaction between physiological changes during pregnancy and the pathophysiology of inflammatory bowel disease.

cytokine profile and less stable microbiome compared to patients with UC, where Th2 responses appear more prevalent. Pregnancy modulates these disease-underlying mechanisms to a different extent at different timepoints during gestation, which may further explain why disease modification is not always apparent. Nevertheless, several conclusions may be inferred from our current understanding of pregnancy-induced physiological changes. Overall, a beneficial effect of pregnancy on epithelial barrier function seems apparent, with relatively small fluctuations of pregnancy hormones already affecting the gut barrier. Furthermore, an overall image of induction of tolerance and suppression of immune responses during gestation is arising. With a predominant shift toward a Th2 phenotype, many reviews have speculated that, in particular, Th1-mediated diseases such as RA and CD may benefit from these pregnancy-induced changes, whereas Th2-mediated diseases (such as SLE and UC) might be negatively affected (6,153,154). HCG, estrogen, and progesterone rise rapidly during pregnancy and have shown several anti-inflammatory actions in animal models. Although most of these changes would be compatible with improvement of IBD activity, it has also been demonstrated that pregnant patients with SLE have lower levels of estrogen and progesterone in the third trimester of pregnancy compared to healthy controls, suggesting that some patient groups may benefit less from rises in pregnancy hormones (155). This also might be the case in UC, but studies to support this hypothesis are lacking. Finally, changes in the microbiome occurring during normal pregnancy do not appear to be beneficial to patients with IBD, but again, it is unclear to what extent these changes are modulated by pregnancy hormones and to what extent microbial alterations are present in pregnant patients with IBD. Thus, immune regulation in both pregnancy and IBD are complicated and not static. Whether or not IBD course is affected by pregnancy may depend on individual patient's characteristics, including ongoing disease activity before conception, their microbiome and hormone/diet-induced changes therein, and genetic underlying risk factors. Predicting which patients may experience reduced disease burden or increased disease activity during pregnancy and postpartum requires a better insight into the physiology and pathology of pregnancy and IBD.

CONFLICTS OF INTEREST

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