Ulcerative colitis: effect on fertility and pregnancy

Ouzounıdou A, Koukourikos K, Kourkouta L, Tsaloglidou A.*

Department of Nursing, Alexander Technological Educational Institution of Thessaloniki, Greece

ABSTRACT

Introduction: Ulcerative colitis is one of the most interesting nosological entities of gastroenterology and internal medicine. This chronic autoimmune disorder of the digestive system, along with Crohn's disease, is a type of idiopathic inflammatory bowel disease. It mainly affects people during their peak reproductive age, i.e., 15 to 30 years old. It is characterized by diffuse mucosal inflammation of the large intestine, which is limited to the colon and shows alternating periods of exacerbations and remissions.

Purpose: To review the world literature regarding the impact of the disease on fertility, the course of pregnancy, and consecutively, the outcome of pregnancy.

Materials and methods: An extensive review of the recent national and international literature in electronic databases (Pubmed, Google Scholar) and in scientific journals was accomplished through the use of appropriate keywords.

Results: The majority of women will have a chance of conceiving. For about 25% of them, conception will be achieved in the course of the disease and it will progress normally, resulting in a healthy fetal outcome. Infertility only occurs among men while they are taking medicines, whereas among women it occurs after surgery for ileoanal anastomosis. During periods of flare-ups, there is a possibility of spontaneous abortion, premature labor and birth of an infant with low birth weight. The majority of pharmaceutical formulations can be used safely both before and after pregnancy without causing any birth defects**.**

Key words: Ulcerative colitis, inflammatory bowel disease, pregnancy, fertility, reproduction

***Corresponding author**:
Tsaloglidou Areti
Clinical Nurse Lecturer, Department of Nursing
Alexander Technological Educational Institute of Thessaloniki, Greece
Tel: +30 6948377619
e-mail: aretitsa2010@hotmail.com

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INTRODUCTION

Ulcerative colitis and Crohn's disease are referred to in the literature as idiopathic inflammatory bowel diseases (IBD). Since IBD are chronic gastrointestinal disorders, they are often accompanied by local and systemic complications. Pregnancy usually worsens these diseases, and, on the other hand, these diseases may negatively affect the smooth course of pregnancy. This interaction between pregnancy and IBD is mainly the result of immunological changes occurring during a normal ongoing pregnancy and also the result of the immunological profile of these diseases [1].

Ulcerative colitis mainly occurs at a young age, at a rate of 5% - 14%, when issues, including fertility, pregnancy and plans for creating a family, play an important role in young people's lives. Women with ulcerative colitis have similar rates of conception to those of the general population, unless they have undergone pelvic surgery [2]. In most cases, the disease does not affect the woman's ability to become pregnant. However, the fertility of the male partner can be affected by sulfasalazine (Azulfidine) (one of the drugs used for treatment), since this drug can reversibly reduce sperm counts. This drug causes sperm abnormalities in 80% of men, which are reversible, however, after discontinuation of the drug [3]. Women who have undergone surgery for ileoanal anastomosis have reduced chances of conception. It is reported by Olsen et al (2002) that there is a decrease in fertility up to 80% [4].

Patients who wish to become pregnant should be informed by their physicians of the outcome of pregnancy, as well as of any treatment options during the period before conception, and also during pregnancy [5].

Gynecological disorders often occur among ill women suffering from menstrual disorders with gastrointestinal symptoms overlapping those related to inflammatory bowel disease. Knowledge and understanding of the range of gynecological problems--for example, fistula, or abscess of the perineum or vagina, dysfunctional uterine bleeding , dyspareunia, subfertility possibly due to tubal blockage, and ovarian dysfunction related to bowel disease-- which have been associated with IBD, will assist practitioners in treating these women [6].

Genetics and heredity

Patients worry about passing their disease on to their offspring. Unfortunately, family history is the strongest predictor for development of the disease. Although the disease does not follow the Mendelian Pattern of Inheritance, some predetermined genetic factors contribute to the sensitivity of the disease [7]. According to Zeglinas et al. [8], 14% of patients with ulcerative colitis have a positive family history. If a parent is affected, the risk of the offspring developing the disease is 2-13 times higher than in the general population, and it is estimated that, among first-degree relatives, it reaches 1.6%. In addition, if both parents suffer, the risk of their offspring developing the disease is estimated to be 36% [9].

Ulcerative colitis and fertility

Infertility is defined as the diminished ability or inability to conceive and have an offspring. It is also considered as the failure to conceive after a year of regular intercourse without contraception [9]. Overall, about 25% of women will conceive during the disease and most of them will have a normal pregnancy and healthy children [10]. Fertility among ill women is similar to that of their healthy peers, unless there is a preexisting pelvic surgery, or possibly an acute exacerbation of the disease [2]. Before surgery, age is the only independent factor affecting fertility rates, as in the general population [11]. However, voluntary childlessness, dyspareunia and the fear of having a sick child, result in the increased use of contraception and in the creation of smaller families at a rate of 82% after diagnosis of the disease, compared to the general population [12]. Active inflammation of the colon and any scarring or inflammation with direct involvement of the fallopian tubes or ovaries, have been shown to reduce fertility. Women who have had any surgical resection are at risk for adhesions, which may also affect the function of the fallopian tubes. The rates of infertility are about 26-48% among patients who have undergone surgery in comparison with those who have not, whose rate is about 12-15% [13-14]. Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) has been shown to increase dyspareunia and it can significantly reduce fertility [4]. Therefore, some minimally invasive alternative techniques can be used prior to conception. Such techniques include colectomy with ileo-rectal anastomosis, or partial colectomy with creation of temporary ileostomy and postpartum completion of the surgery with ileo pouch-anal anastomosis, as well as the use of laparoscopic surgery among patients of reproductive age, in order to avoid the formation of adhesions [15-16]. However, the majority of these patients can conceive with in vitro fertilization (IVF) [17].

Men who take sulfasalazine have reduced fertility or infertility, which is reversible after two months off medication, and it should be replaced by 5-ASAs at least four months prior to conception [18]. This substance appears to cause seminal disorders (oligospermia, reduced sperm motility and abnormal morphology) and infertility in 60% of men [19]. Replacement of this substance with mesalazine seems to also restore male fertility [20]. In addition, methotrexate has been demonstrated to be teratogenic [21]. It is also associated with oligospermia, but there is no evidence, however, that

it causes any birth defects. Nevertheless, its use must be ceased at least four months prior to conception [22]. Azathioprine does not affect fertility, but it may have a teratogenic action [23]. Infliximab increases sperm volume, but it also results in a reduction in the mobility of spermatozoa [24].

Care before pregnancy

Every woman with ulcerative colitis who has the possibility of pregnancy in mind should follow the following recommendations prior to conception:

- Ensuring patient's vaccination (hepatitis A and B, pneumonia, influenza and tetanus / diphtheria / pertussis) and monitoring for any signs of colon cancer and dysplasia and cancer of the cervix [25].
- Routine laboratory tests, including complete blood count, vitamin B12, folate and iron levels, should be performed. In addition, control of vitamin D and of transglutaminase levels of the tissue should be carried out, especially if the patient has difficulties in conceiving, since abnormal levels are associated with infertility [26]. A supplement containing at least 400mcg of folic acid should be taken, since it can reduce the risk of this specific deficiency at birth. Drug intake should be initiated prior to any attempt of conceiving and should be continued at least until the end of the first trimester of pregnancy [3].
- Smoking, drinking, or use of any narcotic drug should be discontinued before any attempt of conceiving.
- Women taking medication or using nonprescription drugs should reconsider their intake in collaboration with the health care institution, since some of these drugs are safe during pregnancy while others are inappropriate. In some cases, an alternative medication may replace an unsafe drug.
- Caffeine intake should be limited to less than 250mg per day, both during the period of conception effort and during pregnancy.
- Finally, a hematological test for rubella (German measles), varicella (chicken pox), HIV, hepatitis B and hereditary genes, e.g. cystic fibrosis, might be recommended before pregnancy [3].

Ulcerative colitis during pregnancy

A number of initial studies conducted suggested that women diagnosed with ulcerative colitis during pregnancy had poor prognosis [27]. Data have changed ever since. The activity of the disease at the time of conception is of great importance for the course of the disease during pregnancy. It has been found that, in two thirds of patients with active disease during this period, the disease will remain active or will be aggravated, while remission is expected to occur during pregnancy in one third of patients, especially during the first trimester [28]. If there is a disease flare, stool studies should undergo laboratory testing to exclude the possibility of contamination, especially from *Clostridium difficile*, which is more prevalent during the perinatal period [29]. Conversely, if there is a disease recession at the moment of conception, the disease is likely to remain in remission during pregnancy [30]. Thus, conceiving should be attempted when the disease is in remission [31]. According to a number of studies, women with ulcerative colitis are more likely to be active during pregnancy compared with women suffering from Crohn's disease. This may be due to cytokine production of the placenta and its impact on ulcerative colitis [32]. Surgical treatment, including removal of the colon may be performed during pregnancy, although there is an increased risk of preterm labor or spontaneous abortion. The majority of women who have undergone surgery before conception may have a normal pregnancy and delivery [3].

The effect of ulcerative colitis on the outcome of pregnancy

The current data shows that, when ulcerative colitis is quiescent, it has little effect on the outcome of pregnancy. On the contrary, patients with active disease have higher possibilities of spontaneous abortion, premature labor and infants with low birth weight [33-34]. Preterm labor is associated with the presence of exacerbations of the disease during pregnancy. A cohort study conducted in Denmark showed that the risk of preterm labor is increased if the mother has been hospitalized during her pregnancy and if the first treatment for ulcerative colitis has occurred during pregnancy [35]. A recent European study which included 332 pregnant women from 12 countries and was published in 2011 (survey years 2003-2006) showed that the outcome of pregnancy did not differ significantly between healthy women and women with inflammatory bowel disease [28]. A meta-analysis published in 2007 showed increased rates of preterm labor among women with ulcerative colitis and Crohn's disease and an increased risk of congenital abnormalities among children born from women with ulcerative colitis [14]. However, there are other studies supporting the opposite, where the risk of congenital abnormalities does not seem to be increased [35-36]. In addition, a retrospective study involving 502 undiagnosed pregnant women and 121 pregnant women diagnosed with ulcerative colitis, showed an increased risk of delivery with low birth weight [28]. Patients with ulcerative colitis have a slightly increased incidence of birth by caesarean section compared with the normal population (13.5% and 9.5%, respectively) [37]. Birth by cesarean section was observed more among pregnant women who had

had frequent hospitalizations, while the majority of them were due to the patient's or physician's preference rather than to a true obstetric indication [2].

Disease activity in the course of pregnancy may be controversial. However, pregnancy seems to play a beneficial role in ulcerative colitis in the long term. A large European study completed in 2006 reported that the rates of exacerbation per year decreased from 0.34 to 0.18 after pregnancy [36]. With regard to breastfeeding, it seems that the independent course of the disease is not affected. However, 56% of women do not breastfeed their children due to relevant clinical recommendations, fear of interaction with drugs, or personal choice. Limited data coming from a small number of patients show that Infliximab was not transferred from mother to child through breast milk [38]. This is why it is necessary to discuss the benefits of breastfeeding and the compatibility of various anti-inflammatory and immunosuppressive drugs combined with breastfeeding [39].

Treatment and administrable medicines during pregnancy

The use of medication during conception and pregnancy is of great concern both to patients and to their physicians [40]. Most women do not intend to take any kind of medication when they make efforts to get pregnant. Therefore, the discussion of pharmaceutical options with the patient before conception facilitates the creation of a management plan [41].

A Dutch study found that 61% (51 out of 61) of women planning to conceive consulted a doctor and that about one third of these patients changed medication [42]. The selection of the appropriate treatment should be determined by the following: individual preferences, severity of disease, and potential drug toxicity. Most medicines for ulcerative colitis can be used safely during pregnancy [43].

Generally, the continued use of amino-salicylates during pregnancy is considered to be safe. There are some studies, however, where it is reported that there is a higher incidence of neural tube defects, oral slots and cardiovascular abnormalities [44]. Both sulfasalazine and 5-ASA at doses <3 g / day have not been associated with any increase in congenital anomalies, and women can continue taking sulfasalazine both during pregnancy and during lactation, since it is not associated with an increased risk of pregnancy complications [3,17]. Regarding the use of steroids, some studies have shown that they may be associated with a slightly increased risk of cleft lip or cleft palate among babies of women who have received these drugs per os during the first thirteen weeks of pregnancy [45]. Azathioprine and mercaptopurine are administered to patients who cannot be weaned from these medications and whenever there is any worsening of the disease after their discontinuation. This is always done with the written consent of the pregnant woman, since some studies have shown that they may cause miscarriages and birth defects [22]. Corticosteroids are thought to be safe throughout pregnancy in doses of 15mg per day [15].

Higher doses increase the risk of infection and preterm labor [46]. Cyclosporine crosses the placenta, but its levels are rapidly cleared from the neonate and there are no known teratogenic effects [47]. However, a meta-analysis showed that cyclosporine tends to reduce birth weight and the duration of pregnancy [48].

Anti-TNF agents have been suggested to play an important role in miscarriage. However, evidence from basic science demonstrates that they may be useful in patients who cannot conceive, thus showing that these drugs might have pre-reproducible results [49]. There are no teratogenic effects from the use of these drugs, but the data is limited; therefore, they should only be used if this is necessary. Anti-TNF agents may be used, if necessary, up to the second trimester of pregnancy [50]. Women who are aware of the risk of using drugs compared with the risk of disease activity on the outcomes of pregnancy are more likely to continue taking the appropriate medication during pregnancy [42].

CONCLUSIONS

Patients with ulcerative colitis have normal fertility, except for women who have undergone extensive colectomy and men receiving sulfasalazine. The creation of smaller families is mainly due to voluntary childlessness and to the fear of birth of a child who is going to be sick. Before every pregnancy, some recommendations regarding the use of medications and the execution of certain tests should be followed. Before conceiving, the objective is to achieve remission of the disease. Pregnancies during periods of exacerbations are associated with premature births and spontaneous abortions. It is necessary for the parents to discuss the whole procedure of delivery with their doctor, i.e. if it will take place normally or if it will be carried out by caesarean section. The latter is preferred after an extensive colectomy and ileoanal anastomosis, since adhesions are likely to be created. Continuation of the medication should be discussed both before and after pregnancy. The majority of medicines can be used safely since they are not associated with any congenital anomalies.

Conflicts of interest

The authors have declared no conflicts of interest.

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