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Original article

Pregnancy and inflammatory bowel disease in Greece: A prospective study of seven cases in a single hospital setting

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SUMMARY

Objective: Taking into account the relative confusion in the literature concerning the influence of pregnancy on the underlying inflammatory disease and vice versa, as well as the influence of drugs on the foetus and the gestation itself, we performed this prospective study, as data regarding this important clinical issue in Greece, are lacking. Patients and Methods: Prospective follow-up study of 7 pregnancies in 7 women with previously established IBD, 3 with ulcerative colitis and 4 with Crohn's disease. Results were compared to those of 7 women with inflammatory bowel disease (IBD) with similar clinicoepidemiological data but without gestation (disease control group), and 14 healthy pregnant women (healthy control group). Results: a) Patients with IBD and gestation vs healthy control group: Significantly impaired body weight in newborns from IBD mothers compared to healthy women (2,735+/-869g vs 3,215+/-613g, P=0.06) was found. Significantly more cases of spontaneous abortion or premature delivery in pregnant women with IBD compared to healthy pregnant women (3/7(43%) vs 1/14(7%), P=0.049) were also noticed. Concerning drug consumption it was noticed that azathioprine was taken regularly in one case of spontaneous abortion and in one case of premature delivery. No significant differences concerning other parameters such as smoking habit and death of foetus were observed. b) Patients with IBD and gestation vs patients with IBD without gestation: No significant differences in the history of various parameters of the disease (number of operations, presence of fistulas), previous gestations, and course of the disease during gestation were found. c) Course of the disease six months after delivery: No significant differences between patients with IBD and pregnancy and disease control group were noticed. Conclusion: It is concluded that the course of gestation in Greek women with IBD is accompanied by some unwanted events such as premature delivery, spontaneous abortion, and reduced body weight of the newborn. Clinicians must bear in mind the possibility of the appearance of some unwanted events in pregnant women with IBD during their gestation.

Key Words: Ulcerative colitis, Crohn's disease, Inflammatory bowel disease, Pregnancy, Outcome

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INTRODUCTION

Ulcerative colitis is a chronic inflammatory bowel disease. The onset peaks at age 15-30 years and coincides with the reproductive period[1]. Overall, around 25% of women with inflammatory bowel disease (IBD) will conceive during their disease and most of them will have a normal pregnancy and healthy children[2]. However, specific problems may arise related to these pregnancies.

Crohn's disease also affects women of childbearing age.[3] Available data on Crohn's disease and pregnancy suggest that women with Crohn's disease can expect to conceive successfully, and carry to term and deliver a healthy baby,[4] although data from different countries do not completely agree with this assumption.[5]

It is common sense that young couples are often concerned about the potential effects of IBD on fertility, pregnancy, and the foetus.

Taking into account the relative confusion in the literature regarding the influence of pregnancy on the underlying IBD and vice versa as well as the influence of drugs on the foetus and the gestation itself, we performed this

prospective study as data regarding this important clinical issue in Greece, are lacking.

PATIENTS AND METHODS

We prospectively studied 7 women with IBD aged 34.7+/-2.4 years (3 with ulcerative colitis and 4 with Crohn's disease), who became pregnant while the underlying IBD was quiescent. Drugs consumed during gestation were: mesalazine 3 patients, concurrently mesalazine and azathioprine 1 patient, azathioprine 1 patient and without treatment 2 patients. Fourteen healthy pregnant women matched for age (aged 33.4+/-2.8 years - healthy control group) and 7 women with IBD matched for age as well as for the type, extent and duration of disease, without gestation (aged 33.3+/-2.6 years - disease control group), served as control groups. Smoking habits, duration of gestation, outcome of IBD, mode of delivery, demographic characteristics of newborn, and the presence of congenital abnormalities, were carefully recorded in both IBD patients and the healthy control group. The clinical course of women with IBD and pregnancy and women with IBD without pregnancy was also evaluated for further six months after delivery.

For statistical analysis Fisher's exact test and Pearson's Chi Square test were used.

RESULTS

a) Comparisons between the group of pregnant women with IBD and the group of normal pregnant women

Smoking habits

The proportion of smokers among the pregnant women with IBD was 43% compared with 14% in the group of normal pregnant women (*P=0.280,* Fisher's exact test, no significant differences).

Body weight of newborn

A trend toward significant differences between the two groups concerning the body weight of the newborn was noticed. (2,735+/-869g vs 3,215+/-613g, *P=0.06*, *Pearson Chi Square test*).

Outcome of pregnancy

Significant differences between the two groups were noticed as far as the outcome of pregnancy (spontaneous delivery and preterm delivery) were concerned (*P=0.049*) (Table 1)

Drug consumption

Azathioprine was taken in one case with abortion (abruption of placenta) and in one case of preterm (37th week) delivery.

Mode of delivery

No significant differences in the mode of delivery (vaginal or caesarean) between the two groups were noticed {(vaginal: 4/6(67%)*(*)* vs 12/14(85%)) or caesarean: {(2/6(33%) vs 2/14(14%), *P=0.329*)}

(*) Excluding a woman with spontaneous abortion

Sex of the newborn

There were 2 male (43%) and 4 female (67%) newborns in the group of pregnant IBD women versus 6 male (43%) and 8 female (57%) newborns in the group of normal women.

Death of newborn

No deaths were noticed in both groups (excluding one abortion in the group of pregnant IBD women).

b) Comparisons between the group of pregnant IBD women and the group of non-pregnant IBD women

Smoking habits

No significant differences among pregnant women with IBD and non-pregnant women regarding the proportion of current smokers was found (3/7, 43% vs 5/7, 66%, *P=0.266*, *Fisher's exact test*)

Fistulizing disease

No significant differences among pregnant women with IBD and non-pregnant women with IBD as far as the percentage of fistulizing disease was concerned (2/7, 29% vs 0/7, 0%, *P=0.462, Fisher's exact test*)

Previous surgery

No significant differences among pregnant women with IBD and non-pregnant women with IBD as far as the percentage of patients with previous surgery was concerned (1/7 vs 0/7), *P=0.408*

Body Mass Index of newborn

No significant differences between the two groups as far as the body mass index was concerned (21.6+/-1.8 vs 23.9+/-3.2) *P=0.131*

Previous gestations

No significant differences concerning previous nor-

Table 1. Outcome of pregnancy

Group	Abnormal gestation (Spontaneous abortion or preterm delivery)	At term delivery	P value (Pearson x^2 test)
IBD with gestation	3/7 (43%)	4/7 (57%)	P=0.049
Normal women	1/14 (7%)	13/14 (93%)	

mal or abnormal gestations were found. {Normal delivery 4/7(57%) vs 4/7(57%) spontaneous abortion 2/7(29%) vs 2/7(29%) and voluntary abortion 1/7(14%) vs 1/7(14%)}

IBD outcome during gestation

The course of the disease in the group of pregnant IBD women was not negatively influenced by the gestation itself. So, among the 7 women with IBD being on remission at the beginning of gestation, all remained so during the whole period of observation. On the contrary, among the 7 women of the disease (IBD) control group 3(43%) remained on remission, 1(14%) relapsed and 3(43%) were in chronically active stage (*P=0.04*) (Table 2).

Outcome of IBD 6 months after delivery

No significant differences in the outcome of IBD 6 months after delivery between the two groups were noticed (remission – remission, remission – relapse, relapse – remission, chronically active disease and chronically active disease – exacerbation) (Table 3).

DISCUSSION

The results of the present study showed that pregnancy in Greek women with IBD is accompanied by some unwanted events including reduced body weight of the newborn and abnormal gestation (preterm delivery and spontaneous abortion). However, the course of the underlying IBD is not influenced by the gestation if the bowel disease was quiescent at the beginning of gestation.

These results are in accordance with others derived from developed countries of Europe and North America. In a recently published multicenter, multinational study referring to 173 female ulcerative colitis and 93 Crohn's disease patients, the rate of spontaneous abortion and caesarean section increased after IBD was diagnosed (6.5% vs. 13%, $p = 0.005$ and 8.1% vs 28.7% of pregnancies, respectively)[6]. Results similar to ours were described in another study according of which, maternal IBD was associated with increased odds of preterm delivery, low birth weight, small gestational age (in Crohn's disease patients), and reports of congenital malformations (in ulcerative colitis patients).[7] In a case-control study of 116 singleton pregnancies with IBD compared to 56,398 singleton controls it was found that IBD was associated with an increased risk for labor induction, chorioamnionitis and Caesarean section, but there were no differences in neonatal outcomes[8]. In the same study subgroup analysis demonstrated an increased risk for low

Table 2. Outcome of IBD during gestation

	Remission	Relapse	Chronically active disease	P value (Pearson x^2 test)
IBD with gestation	7/7 (100%)	0/7 (0%)	0/7 (0%)	P=0.04
IBD without gestation	3/7 (43%)	1/7 (14%)	3/7 (43%)	

Table 3. Outcome of IBD six months after delivery

	Remission - Remission	Remission - Relapse	Relapse - Remission	Chronically active	Chronically active - exacerbation
IBD with Gestation	5/7 (71%)	2/7 (29%)	0/7 (0%)	0/7 (0%)	0/7 (0%)
IBD without gestation	2/7 (29%)	0/7 (0%)	2/7 (29%)	2/7 (29%)	1/7 (14%)

birth weight in the ulcerative colitis group vs the Crohn's disease group.[8]

As far as the incidence of congenital abnormalities appearing in children born to women with ulcerative colitis is concrned no significantly increased overall risk was noticed in a Hungarian study, although an increased risk of some selected abnormalities including limb deficiencies, and obstructive urinary congenital abnormalities, was found.[9]

Another point of interest regarding gestation in IBD patients is the maternal and fetal outcomes of pregnant females undergoing colectomy for ulcerative colitis. Older studies have reported high morbidity and mortality in mothers and their offspring after colectomy for ulcerative colitis during pregnancy. However, in a relevant study which included five females who had undergone an operation (subtotal colectomy with Brooke ileostomy) for fulminant ulcerative colitis while pregnant, it was noticed that all females had successful pregnancies, and no maternal or foetal deaths occurred. Concerning the same matter, review of the literature revealed 37 such cases up to 2006. The overall foetal and maternal mortality was 49% and 22% respectively. Postoperative maternal morbidity was reported in 24%.[10] Today, it seems that subtotal colectomy and Brooke ileostomy for ulcerative colitis during pregnancy represents a safe procedure. However, it is obvious that a multidisciplinary team that includes gastroenterologist, obstetrician, and experienced surgeon is of paramount importance for an optimal outcome.

Pregnancy is also safe in female patients with IBD and ileal pouch-anal anastomosis[11]. Functional results are altered almost exclusively during the third trimester, but pouch function promptly returns to prepregnancy status in most females. A small proportion of females have long-term disturbances in function, but these are not related to the method of delivery. Thus, the method of delivery should be dictated by obstetric considerations.

A significant proportion of patients with IBD receives one or more drugs as a maintenance treatment. In a relevant study it was reported that 48.6% of the patients took medication at the time of conception and 46.9% during pregnancy[6]. The drugs that are in use as a maintenance treatment include sulfasalazine and mesalazine, antibiotics (metronidazole and ciprofloxacine) corticosteroids (including the newer ones), immunosuppressives (azathioprine, 6-mercaptopurine, methotrexate and cyclosporine) and biologic agents (infliximab). In our patients it was found that the use of mesalazine corticosteroids and antibiotics was safe, while the use of azathioprine was accompanied by a premature delivery in one patient and spontaneous abortion in another one.

Despite this finding, the available data concerning the safety of these drugs are in favour of the assumption that all of them including immunosuppressives and biologic agents are of no significant risk for the patient or the mother. In 113 female patients with 207 conceptions none of the drugs used to treat IBD (mesalazine, antibiotics, corticosteroids and immunosuppressives) was associated with poor pregnancy outcomes.[12]

Concerning sulfasalazine and its derivate (mesalazine, 5-aminosalicylic acid), the first line drugs used in the treatment of IBD, no significant increased prevalence of congenital abnormalities in the children of women treated with sulfasalazine during pregnancy was found[13]. However, in another study, an increased risk of stillbirth and preterm birth in women who had been prescribed mesalazine during pregnancy but no substantial increased risk of malformations was noticed[14]. According to the authors of the paper it was difficult to distinguish the specific effects of disease activity and mesalazine use.[14] In our series no increased risk for congenital abnormalities or side-effects on the foetus were noticed. So, sulfasalazine and its derivates appeared to be safe during pregnancy.

Concerning the use of immunosuppressives during pregnancy, their use is believed to be relatively safe. In an interesting study, examining the intrauterine exposure to maternal azathioprine in three patients with Crohn's disease and autoimmune hepatitis, treated with azathioprine throughout all trimesters of their pregnancies, it was found that thiopurine metabolites (6-thioguaninenucleotides and 6-methylmercaptopurine) concentration was slightly lower in the red blood cells of the infant than the mother. The authors concluded that the placenta forms a barrier to azathioprine and its metabolites[15] and this could be of value regarding the possible toxicity of the drug in the foetus. In a large study, 6-MP use before or at conception or during pregnancy appeared to be safe. The authors concluded that discontinuation of the drug before and during pregnancy is not indicated[16]. However, in another study concerning Danish patients an increased risk of congenital malformations, perinatal mortality and pre-term birth in children born to women treated with azathioprine or mercaptopurine during pregnancy, was found[17]. In our series use of azathioprine was associated with unwanted effects in two patients. So, taking into account the conflicting - in some ways - data of the international literature, we can assume that azathioprine during gestation must be used with caution, especially in the first trimester.

Biologic agents are used with increased frequency in the treatment of both active ulcerative colitis and Crohn's disease. In a study involving ten pregnant women with

IBD, eight of them received maintenance infliximab infusions throughout their pregnancy and two received their initial infliximab infusions during pregnancy. No infants had congenital malformations, and intrauterine growth retardation[18]. In another study involving 96 pregnant women with IBD directly exposed to infliximab treatment, live births occurred in 67%, and miscarriages in 15%. Therapeutic termination of gestation was applied in 19% of the pregnancies, proportions that are similar to those expected for the general U.S. population of pregnant women or pregnant women with CD not exposed to infliximab[19]. None of our patients received infliximab during gestation. So, regarding the use of infliximab during pregnancy, we have to consider the benefits of the drug in achieving response and maintaining remission and on the other hand the risk of exposing the foetus to the drug.

In the present study we also examined the course of IBD six months after delivery. It was of interest to see that although IBD remained quiescent during the whole period of gestation, at the end of the 6th month after delivery, a trend toward recurrence was noticed (*P=0.084*), a fact meaning that the possible protective effect of gestation in those patients being at remission at gestation, was diminished. In a recently published large study in which the authors examined the rate of relapse in the subsequent years after delivery, it was found that the rate of relapse decreased in both ulcerative colitis and Crohn's disease patients.[6]

In conclusion, from the results of the present study and the review of the available data of the international literature we can assume that the course of gestation in women with IBD is favorable. However, some untoward effects such as premature delivery, spontaneous abortion and reduced body weight of the newborn can be expected. On the other hand, the course of the underlying inflammatory bowel disease remains unchanged if IBD was quiescent at the beginning of gestation. These results could be of value in Greek women with IBD wishing and planning to be pregnant.

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ADDENDUM

After submission of this article, before publication, an interesting meta analysis concerning the outcome of pregnancy in women with inflammatory bowel disease *(Cornish JA, Tan EK, Teare J, Teoh TG, Rai R, Clark SK, Tekkis PP. A Meta-analysis on the Influence of Inflammatory Bowel Disease on Pregnancy. Gut 2006 Dec 21;)* appeared in the literature. It was a meta-analysis combining studies reporting on pregnancy outcomes related to IBD during a 26-year period (1980 - 2006), with specific data for incidence of ulcerative colitis and Crohn's disease. The authors identified studies describing pregnancy outcome in women with IBD, and they used random-effect meta-analysis to compare outcomes between women with IBD and healthy controls. In 12 studies that satisfied the inclusion criteria, there were a total of 3,907 patients with IBD (1,952 [63%] with Crohn's disease, 1,113 [36%] with ulcerative colitis) and 320,531 controls. They found that compared with controls, women with IBD had a 1.87-fold increase in incidence of prematurity (< 37 weeks' gestation; 95% confidence interval [CI], 1.52 - 2.31; $P <$. 001) and more than double the incidence of low birth weight (< 2500 g; 95% CI,1.38 - 3.19; $P <$. 001). Women with IBD were 1.5 times more likely to undergo Caesarean delivery (95% CI, 1.26 - 1.79; $P <$. 001) and had a 2.37-fold increased risk for congenital abnormalities (95% CI, 1.47 - 3.82; $P <$. 001). Moreover, women with IBD who become pregnant were at a higher risk for premature birth, low birth weight, and Caesarean delivery, whereas risks for stillbirth, small for gestational age, and congenital abnormalities were not significantly increased. Crohn's disease, but not ulcerative colitis, was associated with an increased risk for low birth weight and Cesarean delivery. Finally ulcerative colitis was associated with an increased risk for premature birth and congenital abnormalities. Bearing in mind the above mentioned results, we emphasize the fact that our findings are in accordance with the findings of this metaanalysis, which demonstrated a higher incidence of adverse pregnancy outcomes in IBD patients.