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Case Series

Obstetrics and Gynaecology Section

Management of Inflammatory Bowel Disease and Pregnancy using Prophylactic Low Dose Low Molecular Weight Heparin and Corticosteroids

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ABSTRACT

The circulating nonspecific immune complexes, complement system peptides and auto-antibodies may induce inflammatory/thrombotic events at the placenta and impairment of endometrial receptivity as well as disturbed fetal perfusion in Inflammatory Bowel Disease (IBD) cases. The aim of the case series was to assess the effect of "Low Molecular Weight Heparin" (LMWH) and Low Dose Corticosteroids (LDC) against possible thromboembolic and inflammatory processes happening at the maternal fetal interface and to assess their efficiency in pregnancy outcomes.

Nine cases of IBD, referred during the first trimester of their pregnancies, were retrospectively evaluated {Ulcerative Colitis (UC) (n=7) and Crohn's Disease (CD) (n=2)}. Patients were under aminosalicylate treatment (eight cases mesalamine and one case sulfasalazine) during their admittance to the program and were all in remission. Aminosalicylate treatment was stopped between 8th and 12th gestational weeks and then continued until the appearance of early signs of uterine contractions and/or fetal "discomfort/distress". Following tests for thrombophilia, patients presenting risk factors were included to the study group and were given low dose LMWH (Enoxaparine 1x2000 Anti-XA IU/0.2 ml/day), prophylaxis plus LDC (Methylprednisolone 4 mg/day).

The mean age of the patients was 28.2±4.05 (20-35). No patient had a flare up during their pregnancy. One UC patient with homozygotic Methylenetetrahydrofolate Reductase (MTHFR) 677 polymorphism experienced preterm premature rupture of membranes (PPROM) at the 31th gestational week and was delivered at 32nd gestational week by caesarean section. The other eight cases also delivered between 36-39th gestational weeks by caesarean section due to obstetrical reasons and/or fetal distress. All neonates were discharged from hospital without any complications. Mean gestational age at birth was 258 days (36 weeks 6 days) and mean birthweight was 2772.2±619.3 grams (1530-3670).

In this small case series we were able to obtain successful pregnancy outcomes with the current protocol. Both UC and CD have potential risks of affecting "endothelial/trophoblastic/epithelial" tissues of placenta, impairing endometrial receptivity or fetal perfusion. Control of autoimmune inflammatory processes and thrombotic events by combination of low dose LMWH and LDC may maintain better pregnancy outcome without exacerbation of the IBD.

Keywords: Crohn's disease, Pregnancy immunology, Ulcerative colitis

UC and CD are inflammatory and autoimmune disorders with evidence in favour of genetic predisposition [1-4]. The prevalence of both these diseases are 0.5% with an incidence of 10.7 per 100000 people for CD and 12.2 per 100000 for UC [5,6]. The peak incidence of IBD is between 20-30 years of age [5,6].

These chronic and spontaneously relapsing disorders are characterized by flares of inflammatory processes [4,7]. Humoral immunity {Perinuclear Antineutrophil Cytoplasmic Antibodies (pANCA), Antibodies Against *Saccharomyces cereviscea* Anti-saccharomyces cerevisiae antibody (ASCA) etc.,}, T-cell driven immune responses, inflammatory cytokines, Human Leukocyte Antigen G (HLA-G), environmental factors are the main actors of the disorder [3,4,6]. It is reported that early pregnancy bleedings, protein calorie malnutrition, miscarriages (35% higher rate), preterm deliveries especially with Preterm Premature Rupture of Membranes (PPROM), Intrauterine Growth Retardation (IUGR), pre-eclampsia are more frequent in pregnancies with IBD [7-9]. Cesarean delivery rate is also more higher in these patients [10,11].

Another critical issue is the increased prevalence of Deep Venous Thromboembolism (DVT) among patients with IBD and it has critical impact on pregnancy outcome when such patients become pregnant [7,12,13]. Pregnancy is associated with an increased risk of DVT, which complicates 1-2 of 1000 pregnancies worldwide [14]. This risk increases with IBD patients since IBD is an independant risk factor for DVT. Incidence rate of DVT is reported to be 31.4/10000 person among CD and 10.3/10000 among UC [10,15]. IBD patients have a threefold increased risk of developing DVT compared with individuals without IBD [10,11]. This is thought to be the result of multiple interactions between acquired and genetic risk factors. An imbalance of procoagulant, anticoagulant and fibrinolitic factors predisposing to thrombosis has been reported in patients with IBD [16].

The circulating nonspecific immune complexes, complement system peptides, IgG1 and auto-antibodies may induce inflammatory/thrombotic events at the placenta (intervilous space cellular elements and the endothelial tissue of vascular structures of placenta) and impairment of endometrial receptivity as well as disturbed fetal perfusion [3,7-9]. Although, it is not our primary concern in this study, prophylactic use of low dose LMWH is also beneficial against maternal DVT. Heparin is also claimed to have anti-inflammatory effects [17]. Aminosalicylates and corticosteroids are usually effective in the management of IBD [18-20]. In this small case series, we have tried to investigate the impact of combined use of low dose LMWH and corticosteroids (LDC) against possible thromboembolic and inflammatory processes happening at the maternal fetal interface and to assess their efficiency in pregnancy outcomes.

CASE SERIES

This retrospectively evaluated case series consisted of seven UC and

Case no	Disease	Additional Risk Factors	Treat-ment*	Flare up	Age	Gravida	Parite	Abortion	Gestational age at delivery (week/day)	Birthweight of the new-born (gram)
1	CD	MTHFR 677 Ht	ME	None	29	2	1	0	37/6	2640
2	CD	ANA (+)	SU	None	20	1	0	0	37	3670
3	UC	MTHFR 677/1298 Compound Ht	ME	None	35	2	1	0	35/6	2910
4	UC	APA (+), ANA (+)	ME	None	31	2	1	0	38/6	3380
5	UC	Anti-TPO (+)	ME	None	30	1	0	0	38/6	2970
6	UC	ANA (+)	ME	None	28	2	0	1	37	2800
7	UC	Factor V Leiden Ht	ME	None	27	1	0	0	38/1	2800
8	UC	MTHFR 677 Hm	ME	None	26	4	3	0	31/6	1530
9	UC	MTHFR 677/1298 Compound Ht	ME	None	28	4	1	2	36/3	2250

[Table/Fig-1]: Demographical findings of cases. (CD: Crohn Disease, UC: Ulcerative Colitis).
*ME: Mesalamine, SU: Sulfasalazine, MTHFR: Methylenetetrahydrofolate Reductase, Ht: Heterozygote, Hm: Homozygote, ANA: Anti-nuclear antibody, APA: Anti-parietal Antibody, Anti-TPO: Anti- Thyroid Peroxydase Antibody

two CD cases who were referred to Hacettepe University "Antenatal Care Program" during the first trimester of their pregnancies. All patients were managed within the framework of international protocols. Patients were under aminosalicylate treatment (eight cases mesalamine and one case sulfasalazine) during their admittance to the program and were all in remission. Patients, who were not in remission, were not included in this case series. None of the patients had prior deep vein thrombosis. Aminosalicylate treatment was stopped between 8th and 12th gestational weeks due to possible adverse effects on the organogenesis and then continued until the appearance of early signs of uterine contractions and/or fetal "discomfort/distress". All patients were clinically evaluated (personal history, family history, physical examination etc.,) and laboratory tests for diseases non-specific risk factors were performed (Complete blood count, vitamin B12, Folic acid, liver enzymes, antithrombin-III and protein C activities, activated protein C resistance, lupus anticoagulant, von willebrand factor antigen, Complement 3 and 4, fasting blood glucose, hereditary thrombophilia related polymorphisms; antibodies such as ANA, APA, Anti Smooth Muscle Antibody (ASMA), anti-dsDNA).

Patients presenting risk factor(s) were assigned to "LMWH plus LDC" prophylaxis protocol which is part of our standard approach at inflammatory diseases going together with thrombotic events in pregnant women [21,22]. All of the nine patients of our case series group fulfilled the criteria of this protocol which included low dose LMWH (Enoxaparine 1x2000 Anti-XA IU/0.2 ml/day), LDC (Methylprednisolone 1x4 mg p.o/day). Daily multivitamin complex (Tablet which includes 25 mg vitamin B1, 10 mg vitamin B2, 10 mg vitamin B6, 30 mcg vitamin B12, 100 mg Nicotinamide, 25 mg Cal. Pantothenate, 0.15 mg Biotin and 100 mg vitamin C), folic acid (1x 400 mg/day) and Zinc (1x 25 mg, twice a week) were added to their treatment protocols. Individual based approach was used in the management of the patients. Hacettepe University non interventional clinical research ethics board approval number was GO 16/100.

[Table/Fig-1] shows the demographic, pregnancy and disease specific informations of the patients. The mean age of the patients was 28.2±4.05 (20-35). No patient had a flare up during their pregnancies. Mean gestational age at birth was 258 days (36 weeks 6 days) and mean birthweight was 2772.2±619.3 grams (1530-3670). All patients were under perinatal surveillance program and delivered by cesarean section.

One UC patient with homozygotic MTHFR 677 polymorphism experienced PPROM at the 31th gestational week and was delivered at 32nd gestational week by caesarean section. The neonate was discharged from the neonatal care intensive unit without complication. The other eight cases were also delivered around 37th gestational week (36-39th week) by caesarean section due to obstetrical indications, unsatisfied Doppler Velocimetry findings and non-assuring NST results. Besides the patient with PPROM, there were no other antepartum complications. All of our cases experienced irregular contractions with wide spectrum of cervical changes, non-reassuring Non Stress Test (NST), unexplained bad biophysical scores and unsatisfactory Doppler velocimetry findings after 34-36th gestational weeks although they were all under careful perinatal surveillance and treatment. LMWH, salicylic acid and corticosteroid administrations were stopped at the appearance of early signs of uterine contractions and/or fetal "discomfort/distress". There were no drug related adverse effects on any patient. All neonates were discharged from hospital without any complications.

DISCUSSION

UC and CD are the autoimmune inflammatory disorders presenting with episodes of inflammatory processes followed by periods of remission of the disease [5-8]. Increased risk of obstetrical complications have been reported among IBD patients [7-9]. Intermittent inflammatory activities at the placental maternofetal interface are claimed to be responsible from the dismal outcome [5-9]. It has been reported that autoimmune antibodies bind to human endometrial endothelial cells and impair endometrial angiogenesis by inhibiting the activation of Matrix Metalloprotease-2 (MMP-2) activity [23]. It has also been shown that autoantibodies bind directly to syncytiotrophoblast and disturb apoptotic activities of syncytiotrophoblasts [24-26]. pANCA, ASCA, other immune system complexes and IBD related cytokines most probably attack on: a) endothelial tissue of spiral veins; b) superficial and glandular epithelial cells of the decidua, endothelial cells of the vascular structures of the decidua, endovascular trophoblasts which covers the tip of spiral arteries; and c) syncytiotrophoblasts of chorionic villi (impaired apoptosis of syncytiotrophoblasts and aponecrosis).

Expected results are: 1) the influx of fetal cell (syncytotrophoblasts) degragades into maternal circulation, and activation of T-cell driven immune resposes and "local graft versus host like" reactions; 2) regional and general thrombotic events especially at the venous structures of the placenta (spiral veins etc.,); 3) hormonal immune system response and complement system activation which is also hazardous for maternofetal interface tissues.

All these biological events possibly cause impaired endometrial receptivity and superficial implantation together with impaired fetal perfusion (intrauterine hypoxia). Eventually impaired endometrial receptivity and fetal perfusion may lead to unwanted uterine stimulations/contractions and obstetrical complications. All of our cases experienced irregular contractions with wide spectrum of cervical changes, non-reassuring NST, unexplained bad biophysical scores and unsatisfactory Doppler velocimetry findings after 34-36th gestational weeks although they were all under careful perinatal surveillance and treatment. All patients except one with PPROM were delivered at about 37th gestational week due to obstetrical reasons and/or fetal "discomfort/distress" by caesarean section

in order to prevent unexpected perinatal morbidity/mortality. Mean gestational age at birth was 258 days (36 weeks 6 days) and mean birthweight was 2772.2±619.3 grams (1530-3670). In other words, we have shown that there is a tendency for early onset of uterine contractions.

Humoral immunity changes and T-cell driven immune responses cause obstetrical complications such as early pregnancy bleedings and miscarriages, IUGR, PPROM and preterm deliveries, pre-eclampsia, ablatio placenta among patients with IBD as reported previously [5-9,27-29]. All these obstetric complications and increased prevalence of DVT are the main causes of increased perinatal and maternal morbidity among pregnant women with IBD [12,13].

In our small case series, we have used LDC and low dose LMWH for the management/prevention of "inflammatory disorders related" pathological changes and thrombotic events at the placenta [17,22]. It has been reported that LMWH and LDC can be safely used in pregnancy [21,30]. Eight patients were delivered succesfully without neonatal complications. Only one patient with UC delivered at about 32nd gestational week due to early rupture of membranes and fetal distress. This neonate was discharged from "neonatal intensive care unit" without any complication. In conclusion we were able to achieve a 100 % success rate within a small group.

The adverse impact of IBD on reproduction, pregnancy and DVT deserves to be kept in mind during the perinatal surveillance of IBD cases [7,8,27]. We must also keep in mind the autoimmune character of IBD and adverse effects of circulating antibodies on pregnancy outcome [1,29]. As we do not provide any concrete evidence, our results need to be confirmed by others on higher number of patients.

CONCLUSION

We believe that pregnancies with IBD must be evaluated for additional risk factors for thrombophilia and inflammatory processes. Prophylaxis and treatment with LMWH and LDC protocol appears to be a safe approach in achieving successful pregnancy with continuation of IBD remission.

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