Original Article

Pregnancy and neonatal outcomes in pregnant patients with inflammatory arthropathy treated by etanercept; Retrospective study

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ABSTRACT

Inflammatory arthropathies (IAs) are a group of chronic autoimmune diseases that most commonly affect women of childbearing age. Etanercept is an anti-TNF drug that has been shown to be effective in treating IA patients; however, there is limited data on its safety in pregnant women, especially in Asian countries. This study aimed to evaluate the pregnancy and neonatal outcomes in pregnant patients with IA receiving etanercept. In the present retrospective study, the records of patients with IAs treated with etanercept at Golestan Hospital in Ahvaz during the years 2016-2020 were reviewed and the required information was extracted.

The records of 13 patients (52%) with spondylitis, spondyloarthritis (AS), and 12 patients (48%) with rheumatoid arthritis (RA) were reviewed. Twenty-one patients (84%) had no adverse delivery outcome and 4 patients (16%) had problems during delivery including terminal complication (1 case), abortion (1 case), premature rupture of the bladder (1 case), and pre-eclamptic complication (1 case). Twenty-four patients (96%) had no neonatal complications and 1 patient (4%) had neonatal Intrauterine Growth Restriction (IUGR) complication. In nine patients (36%), cesarean delivery was conducted and in 16 cases (64%), natural delivery was performed. The prevalence of cesarean section and pregnancy and neonatal outcomes were not significantly different according to the type of disease. Based on the results of the present study, it is not possible to make definitive conclusions about the safety of etanercept during pregnancy, and more studies with larger sample sizes are needed.

Keywords: Pregnancy, Neonatal, Outcome, Etanercept, Inflammatory arthropathy

Introduction

Inflammatory arthropathies (IA) is a group of arthritis that is associated with pain, swelling, tenderness to temperature and in the joints, and morning joint stiffness that lasts for an hour [1, 2]. There are several potential causes for self-limiting viral infections to long-term systemic autoimmune diseases for IA [3, 4]. The most common forms of IA are rheumatoid arthritis and Spondyloarthritis (AS). IAs are arthritis caused by an overactive immune system and usually affect several joints throughout the body at the same time [5].

Studies have shown that pregnant women make up a large group of IA patients [1, 6]. Therefore, in addition to the need to monitor the progression of the disease during pregnancy, the drugs administered to treat the disease mustn't interfere with fetal development and maternal health [7]. Etanercept is an anti-TNF drug sold under the brand names EnbrelTM and AltberlTM [8, 9]. It is a fusion of proteins composed of fragment crystallizable (FC) antibodies and two TNF receptors that can inhibit the function of TNF-α in the body, which then prevents it from binding to receptors on the cells, thereby reducing

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inflammation in the body [8, 10].

Nevertheless, cases of kidney damage have been related to the use of this drug. RA patients undergoing therapy with anti-TNFα agents who develop a new onset of renal disease evident a variety of renal pathologic findings, including proliferative lupus glomerulonephritis, pauci-immune necrotizing and crescentic glomerulonephritis (with or without anti-MPO ANCA), and membranous glomerulonephritis with renal vasculitis [11].

According to studies, this drug is administered to treat pregnant IA patients, however, there is not enough information about its effect on fetal development and maternal health. In Iran, no studies have been conducted on the safety of etanercept therapy in pregnancy. Additionally, no specific recommendations for the use of these drugs in IA during pregnancy were suggested. In this regard, this study aimed to evaluate the pregnancy and neonatal outcomes in pregnant patients with IAs receiving etanercept.

Materials and Methods

Study design and population

The present study is a retrospective cross-sectional study that was conducted in 2020 on pregnant women with IAs referred to Golestan Hospital in Ahvaz and treated with etanercept between 2016-2020. Inclusion criteria included being pregnant, aged over 18 years, and receiving etanercept for the treatment of IAs. Exclusion criteria included a history of specific underlying diseases like lung, kidney, and heart and incomplete patient information.

Data collection

Basic characteristics (age, gender, underlying disease, medical history, smoking, medication intake, and Body Mass Index (BMI)) and pregnancy data including gestational age, delivery time, type of delivery (cesarean section / normal), indication for etanercept use (RA, lupus), details related to etanercept therapy, pregnancy and neonatal outcomes, and maternal side effects were extracted from patients' records. Details of etanercept therapy; including when to receive etanercept, medication intake in the first trimester (weeks 1 to 13); the second trimester (weeks 24-27); the third trimester (weeks 28-40), and the duration of etanercept during pregnancy (week) were gathered.

The outcomes of pregnancy include live birth (less than 37 weeks / more or equal to 37 weeks), stillbirth, abortion, premature abortion, preterm delivery (less than 37 weeks), and neonatal outcomes including major and minor birth defects and birth weight (less than 2500 g / more or equal to 2500 g). Maternal side effects during pregnancy including arrhythmia, gestational hypertension, herpes simplex, anemia, hematoma, upper respiratory tract viral infection (yes/no) and severity of complications (serious / non-serious) and their relationship to etanercept (as; related/not related or possibly related/ unspecified) was also investigated.

Statistical analysis

After collection, the data were entered into SPSS statistical software version 22. The data were expressed as percentages and mean ± standard deviation (SD) for categorical and continuous variables, respectively. The comparisons between categorical variables were analyzed using the chi-square test and continuous variables were analyzed using an independent t-test at the significance level of 0.05.

Results and Discussion

The results related to the characteristics of the studied patients (total patients) are shown in **Table 1**. Out of 25 patients studied, 13 patients (52%) had AS, and 12 patients (48%) had RA. The mean age of the patients was 29.80 ± 4.97 years. The mean duration of illness in the studied patients was 2.70 ± 1.08 years. The mean duration of receiving biological drugs in the studied patients was 1.80 ± 0.64 years. Fourteen patients (56%) reported one pregnancy, nine patients (36%) reported two pregnancies and two patients (8%) reported three pregnancies. Moreover, there were four patients with childbirth complications, including one presenting preterm complications, one case having an abortion at 10 weeks, and two patients with premature rupture of membranes (PROM), and preeclampsia, respectively (each one equivalent to 4% of all patients or any equivalent complications) [12]. Out of all participants, 24 samples (96%) did not have any neonatal complications while one patient (4%) had intrauterine growth restriction (IUGR).

Table 1. Demographical information of patients

Variables		Mean ± SD, n (%)
Age, years		29.80 ±4.97
Duration of disease, years		2.70 ± 1.08
Duration of drug use, years		1.80 ± 0.64
Disease	Ankylosing spondylitis	13 (52%)
	Rheumatoid arthritis	12 (48%)
Number of gestation	G1	14 (56%)
	G2	9 (36%)
	G3	2 (8%)
Childbirth	vaginal delivery	9 (36%)
	Cesarean	16 (64%)
Complications of childbirth	No	21 (84%)
	Preterm	1 (4%)
	PROM	1 (4%)
	Preeclampsia	1 (4%)
	Abortion	1 (4%)
Complications of neonatal	No	24 (94%)
	IUGR	1 (6%)

Premature Rupture Of Membranes (PROM), IUGR: Intrauterine Growth Restriction, G1: Number of gestations 1, G2: Number of gestations 2, G3: Number of gestations 3.

The mean age of patients with AS was 27.53 ± 3.61 years, which was significantly lower than the mean age of the group with RA

32.25 ± 5.20 years; (P = 0.014). The mean number of pregnancies in the group with AS was significantly lower than the group with RA (1.07±0.27 versus 2.00 ± 0.60; p=0.001). In the group of patients with AS, five patients (38.5%) had cesarean section and eight patients (61.5%) had a normal delivery. In the group of RA, four patients (33.3%) had cesarean section and eight patients (66.7%) had a normal delivery, which was not significantly different in this regard (p = 0.790).

There was no significant relationship between the childbirth outcomes and the type of disease. In the group of patients with AS, 11 cases (84.6%) had no childbirth outcomes, only one had preterm complications and one case was suffering from preeclampsia. In contrast, in the patients with RA, 10 cases (83.3%) had no childbirth complications, only one had undergone an abortion and one patient showed PORM complications (P=0.404).

No significant relationship was further noted between the neonatal complications and the type of disease (P=0.288). In this respect, in the group of patients with AS, all cases, i.e., 13 individuals (0.100%) were found without neonatal complications. In contrast, 11 patients (91.7%) had no neonatal complications in the RA group and only 1 patient had IUGR **(Table 2)**.

Table 2. Characteristics of patients studied by type of disease

Variables		Ankylosing spondylitis	Rheumatoid arthritis	P-value
Number of gestation		1.07 ± 0.27	2.00 ± 0.60	0.001
Duration of disease, years		2.19 ± 0.84	3.25 ± 1.05	0.014
Duration of drug use, years		1.61 ± 0.54	2.00 ± 0.70	0.20
childbirth	vaginal delivery	8 (61.5%)	8 (66.7%)	0.79
	Cesarean	5 (38.5%)	4 (33.3%)	
Complications of childbirth	No	11 (84.6%)	10 (83.3%)	0.40
	Preterm	1 (7.7%)	0 (0%)	
	PROM	0 (0%)	1 (8.3%)	
	Preeclampsia	1 (7.7%)	0 (0%)	
	Abortion	0 (0%)	1 (8.3%)	
Complications of neonatal	No	13 (100%)	11 (91.7%)	0.28
	IUGR	0 (0%)	1 (8.3%)	

Premature Rupture Of Membranes (PROM), IUGR: Intrauterine Growth Restriction.

The results related to the characteristics of the studied patients by type of delivery are shown in **Table 3**. The mean age of patients with cesarean section was 28.55 ± 4.00 years and the mean age of the group with normal delivery was 30.50 ± 5.44 years which was not significant (P = 0.359). The mean number of pregnancies in the group with cesarean delivery did not show a significant difference compared to the group with normal delivery (1.22 ± 0.44 versus 1.68 ± 0.70) (P = 0.089). There was no significant relationship between the type of disease and the type of delivery. Out of the total number of patients who underwent cesarean section, five patients (55.6%) had AS while four (44.4%) had RA. Of all patients who had a normal delivery, eight patients (50%) had AS while 8 patients (50%) had RA (p = 0.790). There was no significant relationship between delivery outcome and type of delivery (P = 0.076). In the cesarean section group, five patients (55.6%) had no delivery outcome and one patient had a preterm complication, one patient had an abortion complication, one patient had a premature rupture of membranes (PROM) complication, and one patient had a preeclampsia complication [13]. In contrast, in patients with normal delivery, all patients, 16 patients (100%) were without delivery outcome. There was no significant relationship between neonatal complication and type of delivery (P = 0.444). In the group of patients with cesarean delivery, all patients (9 patients (100%) had no neonatal complications since in patients with normal delivery, 15 patients (93.8%) had no neonatal complications and only one patient had IUGR **(Table 3)**.

Table 3. Characteristics of patients studied by type of childbirth

Variables		Cesarean	vaginal delivery	P-value
Number of gestation		1.22 ± 0.44	1.67 ± 0.70	0.08
Duration of disease, years		2.66 ± 1.22	2.71 ± 1.03	0.81
Duration of drug use, years		1.83 ± 0.66	1.78 ± 0.65	0.85
Disease	Ankylosing spondylitis	5 (55.6%)	8 (50.0%)	0.79
	Rheumatoid arthritis	4 (44.4%)	8 (50.0%)	
Complications of childbirth	No	5 (55.6%)	16 (100.0%)	0.07
	Preterm	1 (11.1%)	0 (0%)	
	PROM	1 (11.1%)	0 (0%)	
	Preeclampsia	1 (11.1%)	0 (0%)	
	Abortion	1 (11.1%)	0 (0%)	
Complications of neonatal	No	9 (100%)	15 (93.8%)	0.44
	IUGR	0 (0%)	1 (6.3%)	

Premature Rupture Of Membranes (PROM), IUGR: Intrauterine Growth Restriction.

This cross-sectional study was the first to evaluate the pregnancy and neonatal outcomes in pregnant patients with IA treated by etanercept. According to our findings, no complications were seen in pregnant patients with IA and etanercept intake.

Etanercept is a fusion protein with a monoclonal antibody structure that belongs to the class of drugs that suppress the immune system and TNF-a [14]. Epidemiological studies evaluating the effects of TNF inhibitors, including etanercept, in the treatment of autoimmune rheumatic diseases during pregnancy are limited. Although several case studies and cohorts have been performed in this regard, most of the studies are small and have reported contradictory results [15-17]. In a study by Carman *et al.*, performed on 256 pregnant women with chronic

IA receiving etanercept, 177 (69.1%) deliveries resulted in a live birth, and 81 deliveries (31.7%) resulted in abortions - Stillbirth (spontaneous abortion 21.9%, induced abortion 9%, and stillbirth 0.8%). Of the deliveries leading to live births, 19% had a gestational age of less than 37 weeks (preterm birth). However, the prevalence of complications in these patients was not significantly different from the group with inflammatory arthropathy who were not treated with etanercept or the healthy control group [17]. In the present study, the prevalence of pregnancy outcomes was lower compared to the above study, which is probably due to the small statistical population of the present study (25 people) and demographic differences such as age, duration of medication, duration of illness, the severity of disease, and so on. In a study, Scioscia *et al*. evaluated the pregnancy outcome of two patients with RA who, after recovery with etanercept, decided to continue treatment with etanercept during pregnancy. Long-term study showed control of disease activity and good pregnancy outcomes and no progression of the disease was observed in any of the patients. Finally, they concluded that the use of etanercept during pregnancy and lactation appeared to be safe and had good control over disease activity during this period, which often results in the reactivation of the RA [15]. In another study of 442 patients treated with anti-TNF drugs, three women with RA became pregnant. One of the patients was treated with etanercept and despite the absence of any sonographic abnormalities of the fetus and the satisfactory growth of the fetus at 2.5 months, she decided to discontinue the drug. The other two patients (treated with adalimumab and etanercept) gave birth to healthy infants, however, complications such as prematurity, jaundice, and urinary tract Escherichia coli infection were observed in these two infants [16]. In Verstappen *et al*.'s study, 88 live births (67.69%) were reported from 130 pregnancies in patients who received anti-TNF (etanercept and adalimumab) during or before pregnancy. Spontaneous abortion was 24% in patients receiving anti-TNF medication alone and 17% in patients receiving prenatal medication. Spontaneous abortion was 10% in the control group. The researchers concluded that while the results to date have been promising, the safety of anti-TNF drugs during pregnancy cannot be conclusively determined, and without further evidence, guidelines for avoiding the drug during pregnancy cannot yet be changed [18]. Bröms *et al*. showed that compared to women without anti-TNF treatment, women treated with anti-TNF were at higher risk for preterm delivery (odds ratio 1.61) and the birth of a small baby for gestational age (odds ratio 1.36). The prevalence of preterm labor was higher in women treated with anti-TNF (12.5%) than women without anti-TNF treatment (8.2%) and in the control group (4.6%). Low birth weight was higher in women treated with anti-TNF (14.4%) than women without anti-TNF treatment (10.7%) and the control group (10%) [19]. Several studies have determined the prevalence of pregnancy outcomes in the general population, for example, Linnakaari *et al*. stated that in the general population, approximately 8-15% of clinically confirmed pregnancies result in miscarriage [20]. In the present study, the prevalence of abortion was 1 case (4%), preterm complication (1 case, 4%), premature rupture of the bladder (1 case, 4%) and preeclampsia complication (1 case, 4%), which was similar to the population. However, in a number of other studies that were mentioned, the above complications were more than the general population and more studies should be done in this regard with a larger sample size and with a control group. In the present study, cesarean section was performed in 9 patients (36%) and natural delivery was performed in 16 cases (64%). In the study by Bröms *et al*. (2020), women treated with anti-TNF were at higher risk of cesarean delivery (odds ratio 1.57) than women who were not treated with anti-TNF. The prevalence of cesarean delivery was higher in women under anti-TNF treatment (37.7%) than in women without anti-TNF treatment (27.4%) and in the control group (17.4%). The prevalence of cesarean delivery in women treated with etanercept was 30.9% which was lower than Infliximabb (47.1%) and Adalimumab (40.1%) [19]. The values observed in the present study are similar to Bröms' study. In the present study, the prevalence of cesarean section and pregnancy and neonatal outcomes did not differ significantly according to the type of disease. The duration of the disease and the duration of drug use were not related to cesarean delivery. Due to the low number of complications of pregnancy, it was not possible to determine the frequency of complications according to the duration of medication and the duration of the disease, and it seems that the duration of the disease and receiving the drug had no effect on the complications and consequences.

Limitations of the study

The research design did not allow for repeating the drug administration. It is recommended to conduct multicenter studies with larger sample sizes and with control groups to verify the results.

Conclusion

To sum up, no significant pregnancy and neonatal complications were seen in pregnant patients with IA receiving etanercept. To make definitive conclusions about the safety of anti-TNF drugs during pregnancy, more well-designed studies with larger sample sizes are needed.

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Conflict of interest: None

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Ethics statement: The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, approved all study protocols (IR.AJUMS.REC.1398.857). Accordingly, written informed consent

was taken from all participants before any intervention. This study was extracted from the Internal Medicine Residency thesis of Razi Ghanavati Mohammadi at this university (Thesis#330096280). Besides, ethical issues (including plagiarism, data fabrication, and double publication) have been completely considered by the authors.

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