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Pregnancy outcomes in partners of male ankylosing spondylitis patients treated with anti-tumour necrosis factor-α biologics: real-life results from a single-centre cross-sectional study

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Abstract

Most patients with inflammatory arthritis are at their reproductive ages. Use of anti-tumour necrosis factor alpha (anti-TNF-α) agents, one of the important treatment options for inflammatory arthritis, can cause foetal morbidity and mortality. While most studies on the effects of anti-TNF-α agents on pregnancy outcomes are about maternal exposure, the number of studies on the risks related to paternal exposure is insufficient. This study aimed to assess pregnancy periods and outcomes of the partners of male ankylosing spondylitis (AS) patients receiving anti-TNF-α treatment during the preconception period. Totally, 163 male AS patients using anti-TNF-α agents were identified from the Hacettepe University Biological Registry. Of these patients, 45 (27.6%) who declared that their partners got pregnant after initiation on anti-TNF-α agents were included. Data regarding demographics and drug exposure and pregnancy and infant outcomes were evaluated. Of 45 pregnancies, 39 (86.7%) resulted in healthy live births, 3 (6.7%) resulted in spontaneous abortion, and 3 (6.7%) were terminated with curettage. Of 39 live births, 34 (87.2%) were term and 5 (12.8%) were preterm, 30 (76.9%) had normal birth weight, 6 (15.4%) had low birth weight, and 3 (7.7%) had fetal macrosomia. No congenital malformations related to paternal exposure were observed. This study is valuable as being one of the studies providing pregnancy outcomes of partners of male AS patients receiving anti-TNF-α agents with its relatively high number of patients. The results suggested that paternal exposure to anti-TNF-α agents during preconception period could be safe on pregnancy outcomes.

Keywords Ankylosing spondylitis · Spondyloarthritis · Tumor necrosis factor-α (TNF-α) inhibitors · Pregnancy outcomes · Paternal exposure

Introduction

Anti-tumour necrosis factor-alpha (anti-TNF-α) agents are effective and increasingly used in the treatment of inflammatory arthritis such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Inflammatory arthritis is more commonly encountered in the age of fertility. The pregnancy category of anti-TNF-α agents is category B [1]; nevertheless, data regarding foetal outcomes of maternal or paternal exposure to anti-TNF-α are increasing and there are still major concerns about the effects of these drugs on fertility and pregnancy outcomes particularly in male patients.

Several studies investigating maternal exposure to anti-TNF-α agents have reported controversial results. Earlier studies have suggested increased risks of congenital abnormalities, preterm birth, spontaneous abortion, and low birth

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weight in females having immune-mediated diseases and treated with anti-TNF-α agents [2, 3]. However, these studies have several biases and the definite effect of disease activity on pregnancy outcomes has not been studied substantially. In addition, more recent and large-scale studies have reported anti-TNF-α agents as "safe for pregnancy" [4].

Studies conducted during the first years of the use of the biological agents have mainly focused on the effects of these drugs on sperm in male patients. It has shown that sperm quality is not impaired in males after short- or long-term treatment with anti-TNF-α agents [5–7].

There are several studies reporting no increased risk of miscarriage or malformations, in case fathers are on anti-TNF-α agents during preconception period [8–10]. In a recent prospective multicentre study from Romania, of 202 spondyloarthritis (SpA) male patients, 27 AS male patients exposed to continuous, long-term (range, 12–129 months) monotherapy with anti-TNF-α agents were identified. These patients fathered 30 children from 33 pregnancies and no increases were reported in pregnancy complications or congenital malformations as compared with the findings of general population [7].

Pregnancy process and results can be affected by both maternal and paternal reasons. Information on the safety of anti-TNF-α agents is increasing. There is a great need for additional research on birth outcomes and paternal exposures on children's health. Understanding the role of the effects of sperm and paternal characteristics on pregnancy outcomes before conception plays an important role in determining the effects of drug use on birth outcomes. The aim of this study is to assess the pregnancy periods and outcomes of the partners of male AS patients receiving anti-TNF-α treatment during preconception period and to contribute to the literature by presenting a real-life data. Further data on this subject will be met with both necessary and relevant attention.

Patients and methods

Study population

The patients were enrolled from the Hacettepe University Biological Registry (HUR-BIO), which was established in 2005 and includes more than 3500 patients with inflammatory arthritis (1756 patients with SpA, 992 (56.5%) of whom were males). A total of 163 male AS patients who were using anti-TNF-α were identified from the HUR-BIO. The patients were first asked whether their partners got pregnant after they were initiated on anti-TNF-α agents. Accordingly, 45 male AS patients whose partners got pregnant after the initiation of anti-TNF-α agents were included in the study. The study flowchart for patient enrolment is presented in Fig. 1. The study was conducted from June 2015 to June 2016 in accordance with the Declaration of Helsinki and after obtaining the approval of the Hacettepe University Ethical Committee (Approval number: GO 15/325-11, date: 10

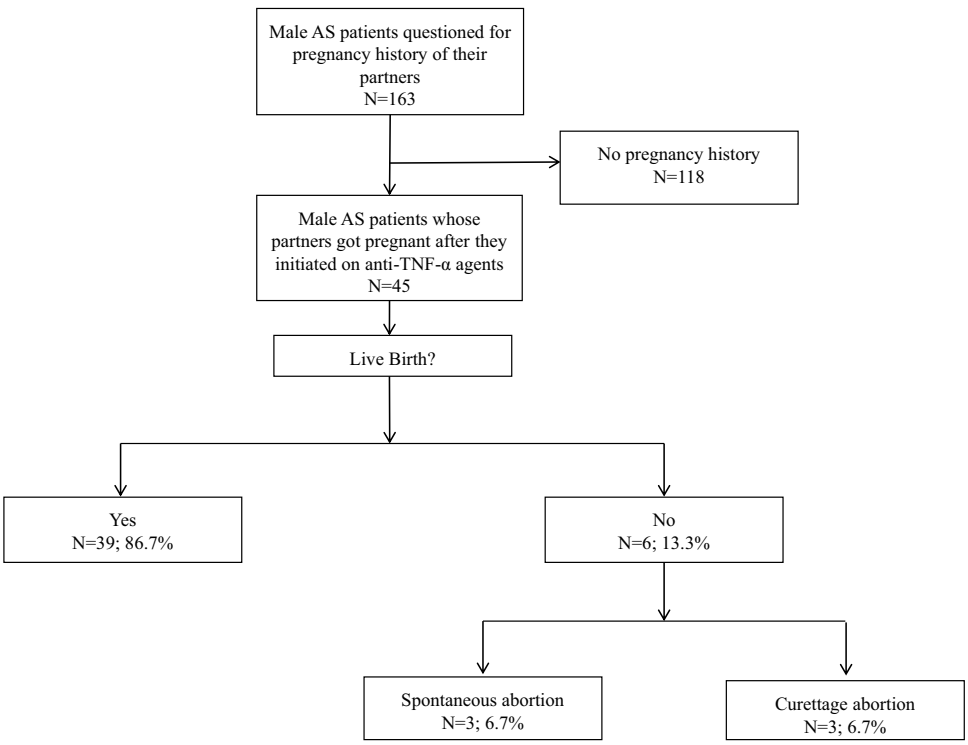

Fig. 1 Study flowchart for patient enrolment and pregnancy outcomes. *AS* ankylosing spondylitis, *anti-TNF-α* anti-tumour necrosis factor alpha

June 2015). Informed consent of all patients was obtained for their participation in the study.

Evaluation of pregnancy and infant outcomes

A questionnaire was performed to all patients. The patients were evaluated for the following parameters: data on demographics and drug exposure; pregnancy process including preconception period, pregnancy plans, SpA disease activity using the bath ankylosing spondylitis disease activity index (BASDAI), and drug cessation; pregnancy outcomes including childbirth and delivery methods (spontaneous vaginal delivery, caesarean section, spontaneous abortion, curettage abortion, and stillbirths); and infancy outcomes including gestational age at birth (< 37 weeks [preterm], 37–42 weeks [term], > 42 weeks [post-term]), birth weight (low [< 2500 g], normal [2500–4000 g], high [> 4000 g]) and congenital malformations.

Statistical analysis

Data analyses were performed using the IBM SPSS Statistics for Windows Version 20.0 software (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov, skewness, and curtosis) to determine whether or not they are normally distributed. The data of descriptive analysis were expressed as the median, interquartile range.

Results

Data on demographics and drug exposure

The mean age of the male AS patients ($n = 45$) was 36.4 ± 5.3 years and the median disease duration was 10 (9) years. The median duration of anti-TNF-α usage (the duration between the onset of anti-TNF agent and the date of the patient included the study) was 60.8 (48.9) months. The median duration of the drugs exposure from the beginning of the treatment to the partners' pregnancy was 19.5 (24.5) months. The distribution of used anti-TNF-α drugs was as follows: infliximab ($n = 19$, 42.2%), etanercept ($n = 13$, 28.9%), adalimumab ($n = 8$, 17.8%), and golimumab ($n = 5$, 11.1%). Moreover, three patients used sulphasalazine during the conception period.

Preconception period

Among 45 pregnancies, 10 (22.2%) were not planned. In addition, 26 (57.8%) patients did not share their pregnancy plans with their rheumatologists. The BASDAI scores of 16 (35.5%) patients were available at the preconception period; the BASDAI score was higher than 4 in 2 (12.5%) of 16 patients. Furthermore, 9 (20%) patients stated that they had active disease during the preconception period.

Pregnancy outcomes

Of 45 pregnancies, 39 (86.7%) resulted in live births, 3 (6.7%) resulted in spontaneous abortion, and 3 (6.7%) were terminated with curettage. The pregnancy outcomes are summarized in Fig. 1. The male AS patients whose partners underwent spontaneous abortion were receiving infliximab, golimumab, and etanercept ($n = 1$ for each). The male AS patients whose partners pregnancies were terminated with curettage were receiving adalimumab, infliximab, and etanercept ($n = 1$ for each); no information was available on the indications for curettages.

Infant outcomes

The median gestational age at birth was 39 (2) weeks. Of 39 live births, 34 (87.2%) were term and 5 (12.8%) were preterm. There were no post-term births. The births weeks of preterm pregnancies were 29, 33, 35, 36, and 36. The median birth weight was 3218 (583) g. Of 39 live births, 30 (76.9%) had normal birth weight, 6 (15.4%) had low birth weight, and 3 (7.7%) had fetal macrosomia (Table 1). No congenital malformations related to paternal exposure were found. The newborn fathered by one of our male AS patients (age, 35 years), who was using adalimumab during the pregnancy period of his partner, had normal gestational age at

Table 1 Demographic and clinical characteristics of 39 live births in partners of male ankylosing spondylitis patients treated with anti-tumour necrosis factor alpha

Infant outcomes	
Gestational week at birth, median (IQR)	39 (2)
Birth weight (g), median (IQR)	3218 (583)
Congenital malformation, *n* (%)	0 (0)
Stay in ICU after delivery, *n* (%)	5 (12.8)
Type of delivery, *n* (%)	
Spontaneous vaginal	13 (33.3)
Caesarean section	26 (66.6)
Birth weight, *n* (%)	
Low (< 2500 g)	6 (15.4)
Normal (2500–4000 g)	30 (76.9)
High (> 4000 g)	3 (7.7)
Gestation week, *n* (%)	
Preterm (< 37 weeks)	5 (12.8)
Term (37–42 weeks)	34 (87.2)
Postterm (> 42 weeks)	0 (0)

IQR interquartile range, *ICU* intensive care unit

birth and normal birth weight but was then diagnosed with Angelman syndrome. Five (12.8%) of 39 live births were hospitalized in the intensive care unit (ICU) after delivery. The fathers of these five newborns were using infliximab ($n=2$), etanercept ($n=2$), and golimumab ($n=1$) during the pregnancy of their partners.

Discussion

In the present study, the pregnancy periods and outcomes of the partners of male AS patients who were receiving anti-TNF-α treatment during the preconception period were evaluated. The study included 45 male AS patients with a median anti-TNF-α exposure of 5 years (60.8 months) whose partners got pregnant after initiation of anti-TNF-α agents. It was observed that one out of every five pregnancies was unplanned and about 60% of these patients did not share their pregnancy plans with their rheumatologists. This finding suggested that unlike in female patients with SpA, a doctor–patient relationship could not be established for discussing a planned pregnancy in male patients and accordingly some cases were overlooked. In our knowledge, there is not sufficient data in the literature about this situation, and in the current practice, doctors' behavior on this subject has not yet fully understood. Thus, we recommend that all patients, irrespective of sex, should be informed in each visit about the pregnancy and treatment process before being initiated on or while using anti-TNF-α agents.

In the present study, the rate of pregnancies resulted in spontaneous abortion or were terminated with curettage was 13%; a finding that was consistent with those in the general populations. In the literature, a cohort study has reported the spontaneous abortion rate to range from 0 to 14% including any patients exposed to anti-TNF-α agents before or during the pregnancy period [11]. In a population-based prospective study from China, spontaneous abortion rates were reported to range from 8 to 20%, with 13–26% of them being associated with undetectable pregnancies [12].

It has been estimated that worldwide, 11.1% of all live births in 2010 were born preterm (14.9 million babies) [13]. In a prospective, comparative, observational study, the rate of preterm delivery was reported to be 3.4-fold higher in the anti-TNF-α group than in the non-exposed group and this increase was suggested to be likely associated with the underlying diseases [14]. Studies have shown that there is a significant relationship between anti-TNF-α exposure and low birth weight [3, 14–16]. In the present study, the preterm birth rate was 12.8% and the low birth weight rate was 15.4%.

To our knowledge, there is no enough data in the literature indicating the causes and rates of neonatal ICU admissions associated with anti-TNF-α exposure. In our study, 5 (12.8%) of 39 live births were hospitalized in the ICU after delivery. No congenital malformations in relation to paternal exposure were observed; only one term newborn with normal birth weight fathered by one of our male AS patients using adalimumab during the pregnancy period of his partner was diagnosed with Angelman syndrome. We are in the opinion that it would be very controversial to report Angelman syndrome, which is a maternal inherited syndrome caused by microdeletion, gene mutation and imprinting defect, may be associated with paternal anti-TNF-α therapy.

Although there is a great need for additional research on birth outcomes and paternal exposures on children's health, studies have shown that many factors, such as a father's preconception environment, diet and mental status, may have an impact on offspring [17]. Understanding the role of the effects of sperm and paternal characteristics on pregnancy outcomes before conception plays an important role in determining the effects of drug use on birth outcomes. Therefore, initial studies conducted during the first years of the use of biological agents have mainly focused on the effects of these drugs on sperm characteristics in male patients.

The possible mechanisms by which anti-TNF-α agents will affect the pregnancy outcomes after paternal exposure are as follows; (1) deterioration of spermatocytes; (2) absorption of drugs or metabolites in the seminal fluid through the vaginal mucosa or a direct effect on the uterus (3) effects of drugs or metabolites on sperm maturation [10, 18].

Studies showed that TNFα is normally produced by germ cells in testes and play an important role in maintaining testicular function and male fertility [19]. It has been reported that TNF-α increases in seminal fluid and has negative effects on spermatogenesis under inflammatory conditions such as AS [20]. Anti-TNF treatment can reduce the levels of TNF and improve spermatogenesis.

Although it was reported that anti-TNF-α treatment had negative effects on spermatogenesis in the first years [21–23], prospective studies in the following years showed that sperm quality was not affected in patients receiving anti-TNF-α treatment [5, 7, 8, 24].

In a prospective study, monitoring sperm parameters in patients with active AS prior to and after 3–12 months of anti-TNF-α therapy; exposure of 20 patients to 3 different types of anti-TNF-α agents did not have a negative impact on sperm quality after 3–6 months and in 6 cases after 12 months of treatment [5].

Also in a recent prospective study; normospermia has shown in sperm analysis of five patients who fathered five healthy children before and after long-term exposure to adalimumab [7].

Puchner et al. did not found any documentation of miscarriages or physical abnormities associated with anti-TNF-α treatment and paternity. Instead, an improvement in sperm

motility and vitality during anti-TNF-α treatment was shown in that review. The authors suggested that the improvement might be due to a decrease in disease activity [8].

In 2010, Villiger et al. studied the effects of anti-TNF-α agents (infliximab, etanercept, and adalimumab) on spermatogenesis in SpA patients (11 patients not receiving therapy and 15 receiving therapy) [24]. They concluded that sperm abnormalities were present also in SpA patients not receiving anti-TNF-α therapy and in healthy controls ($n = 102$) and that the patients on anti-TNF-α therapy had significantly better sperm motility and vitality as compared with untreated SpA patients. Accordingly, continuation of anti-TNF-α therapy was suggested in case of planning a fatherhood [24].

Although no deterioration in spermatogenesis has been shown, it is not clear whether chromosome changes or any unknown effects have been demonstrated by anti-TNF-α treatment. In the present study, no data were available about spermiogram of the patients.

Following the above-mentioned initial reports, most studies have focused on real-life experiences. In the TREAT registry, there were no significant differences among exposure group Crohn's disease patients treated with infliximab or not treated with infliximab or any other biologic agent—in terms of the proportion of healthy infants, congenital abnormalities, live births, spontaneous or elective abortions, and extended hospitalization of newborns [25]. In the nationwide cohort study by Larsen et al. in Denmark, the paternal preconceptional use of anti-TNF-α agents for rheumatic, gastrointestinal (inflammatory bowel disease), and dermatologic diseases was reported to be safe in terms of pregnancy outcomes including congenital abnormalities, preterm birth, and small for gestational age (SGA) [10]. Nevertheless, they also noted that, although not statistically significant, the increased risk for SGA should be taken into consideration [10]. In a recent prospective study from Romania, of 202 SpA male patients, 27 male patients with AS (according to positive radiographic criteria) who were exposed to continuous, long-term (range, 12–129 months) monotherapy with anti-TNF-α agents were identified [7]. These patients fathered 30 children from 33 pregnancies and no increases were reported in pregnancy complications or congenital malformations as compared with the findings of general population [7]. In that particular study, all children were born healthy with normal birth weight, there were no stillbirths, and preterm birth rate was reported to be higher than in the general population (20% vs. 11.1%) [7]. The findings of the present study were similar to and consistent with the findings of this prospective study.

As a result, no adverse effects were observed in men treated with anti-TNF-α agents causing sperm quality or other additional anomalies.

The present study has some limitations. As this study was retrospective in nature, the demographic data of the partners of male AS patients were not available. A number of factors related to the partner (such as age, drug usage, previous pregnancy history, placenta previa, genital infections etc.) that may affect the pregnancy process and outcomes (gestation week at birth, prematurity, birth weight, live birth, low curettage rate) might be overlooked. Although we ask patients in detail; the male patients who answered the question about their partners being pregnant in the period of their anti-TNF treatment might not disclose the data to the physician if their partner got an abortion or D&C. Moreover, no data were available about spermiogram of male AS patients. In addition, data on disease activity of the patients were limited; therefore, the effects of disease activity on the pregnancy outcomes could not be analysed. Unfortunately, lack of a valid control group limits interpretation. Using the data of the general population or the patients on non-biologics (DMARDs, NSAİDs, etc.) whose partners got pregnant, as a control group, could be more beneficial to see clearly the effect of biologics.

In conclusion, the present study is valuable as being one of the studies providing pregnancy outcomes of partners of male AS patients receiving anti-TNF-α agents with its relatively high number of patients. The findings of the present study were in line with those of the studies evaluating the pregnancy outcomes of the partners of the male patients treated with anti-TNF-α agents. Our results suggested that anti-TNF-α drugs could be safe following paternal exposure.

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Author contributions All co-authors satisfy all four criteria (participated in study design, data collection, analysis, interpretation and writing equally), and take full responsibility for the integrity of the study and the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no potential conflicts of interest.

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