# Pregnancy outcome in couples with males exposed to long term anti –TNF alpha blocker therapies – a prospective study

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**Running head** : Male TNF inhibitors exposure

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**Abstract**

**Objective.** To examine the pregnancy achievement and outcomes in couples where men with spondyloarthritis (SpA) were exposed to tumor necrosis factor inhibitors (TNFi).

**Patients and methods.** Pregnancies of SpA fathers were prospectively collected by 6 Romanian rheumatology centers.

**Results.** Twenty-seven patients achieved 33 pregnancies and fathered 30 healthy children. Three elective abortions (personal reasons) and no spontaneous abortions, preeclampsia/ eclampsia, stillbirths, congenital malformations or pathologies in the children were recorded. Five patients showed normospermia before and after long term TNFi treatment.

**Conclusion.** Pregnancy and child outcome in male SpA patients exposed to long term TNFi therapy was reassuring.

Key words: fertility, men, pregnancy, offspring, TNF inhibitors

## Introduction

A large proportion of spondyloarthritis (SpA) patients are affected during peak reproductive years, rendering therapy with biologic DMARDs (bDMARDs) necessary to control active disease [1]. Recent recommendations have offered strategies for pre-conception counseling and treatment with bDMARDs during pregnancy [2-5]. By contrast, there is still limited data available on the safety of pre-conception use of b DMARDs in men.

Previous studies evaluating fertility, pregnancy and offspring outcome in smaller groups and large male cohorts exposed to bDMARDs reviewed by Micu MC et al 2017 [6], indicate no impairment of spermatogenesis by tumor necrosis factor alpha inhibitors (TNFi). Outcome of pregnancy and offspring compared to non-exposed patients or the general population has been found normal. Drug effects on male fertility require sperm analysis and often include a limited number of individuals [7-12]. Pregnancy and offspring outcome after male pre-conception exposure can be studied based on administrative registries but analysis is made mostly in a retrospective manner, data on disease activity and length of drug exposure are seldom available and pregnancy course in partners is often not recorded [13-15]. Prospective data eliminate these shortcomings. The aim of our study was to examine prospectively pregnancy achievement and outcomes in men with SpA exposed to >12 months of therapy with TNFi including the pre-conception period.

**Patients and methods**

Male patients with an established diagnosis of SpA [16,17] fathering children were prospectively included in the study, at 6 Romanian Rheumatology centers (see author affiliation list). The study was performed between 2012-17, was approved by the ethics committee (N683/20.12.2012 and N2394/3.04.2017) and informed written consent was obtained from patients.

Cases were fathers with TNFi continuous exposure $\geq$ 12 months including the pre-conception period (defined as TNFi exposure according to standard protocols within 3 months before conception). The prospective data collection comprised: demographic data, disease related parameters, pregnancy outcome in female partners and offspring outcome. For comparison of pregnancy outcome with the general population, data were extracted from the ATLAS platform (surveillance software linking diagnosis, investigations and medication mainly for economic reasons) of the 1 st Gynecology Clinic Cluj- Napoca, between the years 2012-17.

A standardized data set was completed for each patient/couple (in case a pregnancy was identified and followed) in all participating centers. All patients had a monthly visit with the

doctor for the receipt of TNFi prescription. Information about fertility treatments and pregnancy occurrence in the couple was obtained at each visit. Sperm parameter analysis before and after long term TNFi exposure was available in 5 patients (in 3 of them, evaluation was made during a previous study ,[10]).

Pregnancy and offspring outcome parameters were collected according to the standard protocols of the obstetrics /neonatology/pediatric units in the hospital.

**Statistical analysis**

The assessment of the normality of data was performed using Shapiro-Wilk test. Descriptive statistics was performed for the continuous and categorical variables and results were expressed as mean ± standard deviation (SD) or number of cases and percent.

**Results**

In the 6 centers, 202 SpA male patients, mean age 30 (range 18-71) years, exposed to TNFi were identified. Among these, 27 men with ankylosing spondilitis (AS, positive radiographic criteria) exposed to continuous, long-term (range 12 to 129 months) mono-therapy with TNFi obtained 33 pregnancies. Thirty healthy children were born and 3 elective abortions (personal reasons) were recorded.

Table 1 presents the demographic and disease related parameters in the case couples.

Table 2 shows the outcome of 33 pregnancies fathered by patients compared to 12142 pregnancies of the general population. No increase in pregnancy complications or congenital malformations occurred in cases. All children were born healthy with a weight ≥ 2500g (range 2800-4400g). A trend for a higher percentage of live births, caesarean section and prematurity was detected in the case group. The 6 premature children were born at week 36 of gestation (5 boys and 1 girl) with a weight range of 3300-3800g.

One patient switched due to loss of efficacy from long-term therapy with Adalimumab to Etanercept 2 months before conception and reached again remission at conception time. Two men changed preconception TNFi exposure in subsequent pregnancies: one from Adalimumab to Etanercept and one from Infliximab to Etanercept . One patient stopped Infliximab two months prior to conception, all other patients followed a continuous TNFi regimen. Five patients

presented normospermia both before TNFi therapy initiation and after 12 months of treatment with standard doses of Adalimumab (Table 3). . In this subgroup 7 pregnancies were achieved, 5 children and 2 elective abortions (personal decision, not because of malformations).

**Discussion**

Our study is the first real life prospective study in fathers exposed to TNFi demonstrating no negative impact on pregnancy and child outcome when TNFi were administered long-term including the 3 months prior to conception.

Sperm analysis of five patients before and after long-term exposure to Adalimumab showed normospermia in all patients who fathered 5 healthy children. This confirms previous studies in patients with AS and PsA where no impairment of spermatogenesis was found after short term and long-term exposure to Infliximab, Etanercept, and Adalimumab [9-12]. Several of these studies showed impaired spermatogenesis before initiation of a TNFi and normalization of the spermatogram during treatment [9,11,12].

The absence of sperm alterations under TNFi therapy is reassuring, however, it neither confirms fecundity nor the absence of chromosome alterations in germ cells. Normal fecundity needs to be confirmed by pregnancy achievement in the couple which depends both on male and female factors. Twenty-six couples included in our study achieved 32 pregnancies within one year of the intention of reproduction indicating normal fecundity. Normal fecundity during TNFi therapy has also been recorded in retrospective case series [7,8].

Three recent registry-based studies investigated pregnancy outcomes fathered by men with rheumatic, gastrointestinal (IBD) and dermatologic diseases exposed to TNFi. They found no increased adverse pregnancy or child outcomes compared to non-exposed, disease matched or non-diseased controls [13-15].

A nationwide study identified 372 children fathered by men treated at least once with TNFi (all types, unknown dose and administration frequency, monotherapy or combined with cDMARDs). Regardless of the paternal disease and the type of combination therapy administered to the father, no statistical difference for congenital abnormalities, preterm birth and small for

gestational age was identified between exposed and non-exposed pregnancies [15].

Prospectively collected registry data evaluating clinical safety outcomes in patients with CD (bi-annual records) identified 59 pregnancies (42 with gestational and 17 with pre-gestational exposure) in partners after paternal exposure to Infliximab, at least one infusion (median number of 3 infusions for gestational and 1 for pre-gestational exposure). Regardless of the disease activity at conception, no significant differences of pregnancy and child outcome were observed compared with a non-exposed disease-matched group for the proportion of live births, spontaneous or elective abortions, preterm birth, healthy infants or congenital abnormalities, or extended hospitalization of newborns. The majority of the partners' outcomes resulted in live births with healthy children across the exposure groups [14]. The data are in line with the results of our study analyzing reproduction after long-term exposure to TNFi in male patients.

Registry data are derived from electronically reported administrative health records or surveillance registries. The strength of registries is collection of large amounts of data on exposure and outcome and generation of a large non-diseased comparator group. Registries often include patients with different diagnoses and pathologies that could influence pregnancy outcomes. Other shortcomings of retrospective data collection are that possible confounders like disease activity, life-style factors, comorbidities, precise record of all medications (often only prescription data are given), duration of drug exposure and drug class may not be included. By contrast, prospective clinical studies provide detailed demographic and disease and therapy related data but are limited by sample size.

Our study has several limitations. The number of TNFi exposed patients and the number of pregnancies is small compared to registries, and the pregnancy outcome data could be chance findings. Enrolment of male patients into a prospective study is time consuming since inflammatory rheumatic diseases have a lower prevalence in comparison to the female gender [1,14]. We did not analyze a disease-matched control group. Patients with milder disease are generally less compliant with medical visits. The comparison group from the general population

lacked data on fecundity and demographic data of fathers and mothers. The strength of our study is the prospective design and that the group of fathers was homogenous regarding diagnosis, and all received > 12 months monotherapy with a TNFi. Indeed, the follow-up of five patients with longitudinal sperm parameter analysis resulting in pregnancy achievement and positive outcome strengthens the study conclusions, showing that normal sperm parameters and fertility/ fecundity preservation is possible in SpA patients after long term TNFi exposure.

**Conclusion**

The prospective analysis of the pregnancy and offspring outcome in patients exposed to long term TNFi (Remicade®, Humira®, Enbrel®) therapy including the pre-conception period is reassuring regarding reproduction capacity and the health status of the offspring. Larger prospective, controlled studies are needed in order to confirm these findings.

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**Table 1. Demographic and disease related parameters in patients and partners**

| Parameter | Fathers | Mothers |
|---|---|---|
| **Race Caucasians** | 27 (100%) | 27 (100%) |
| **Age at conception (years)* (min;max)** | 34.6 ± 5.5 (24;47) | 29.5 ± 3.2 (20;35) |
| **Diagnosis** ¶ | | |
| axial involvement in AS | 19 (70.3%) | 0 |
| axial and peripheral involvement in AS | 8 (29.6%) | 0 |
| PsA^ | 0 | 1 (0.4%) |
| **Disease duration at conception(years)*** | 10.6 ± 5.7 | 4 (1 mother) |
| **Abnormality at laboratory screening or imaging at conception** ¶ | 0 | 0 |
| **In remission at conception (BASDAI)** | 26 (96.3%) | N/A |
| **TNFi dosage and exposures** ¶ | | |
| Adalimumab (Humira ®, 40mg/2 weeks) | 12 (36.4%) | 0 |
| Etanercept (Enbrel ®, 50mg/1 week) | 14 (42.4%) | 0 |
| Infliximab (Remicade ®, 5mg/kg/8weeks) | 7 (21.2%) | 0 |
| **TNFi therapy duration (months)*** | 42.6 ± 26.0 | 0 |
| **Other therapies** ¶ | | |
| NSAIDs δ | 14 (43.8%) | 1 (0.4%) |
| SSZ (+NSAID) | 0 | 0 |
| MTX | 0 | 0 |
| Fertility treatments | 0 | 0 |
| **Exposure to smoking, illicit drugs, toxic agents, drinking habits** ¶ | | |
| smoking ¶ | 3 (11.1%) | 0 |
| drinking habits (occasional)¶ | 27 (100%) | 0 |
| illicit drugs exposure ¶ | 0 | 0 |
| toxic agents exposure ¶ | 0 | 0 |
| **Medical history/ comorbidities** | | |
| History of genital tract infections ¶ | 0 | 0 |
| Epidemic parotitis involving testis in teenage/adulthood ¶ | 0 | - |
| Cystitis during pregnancy §¶ | - | 6 (22%) |
| Varicocele ¶ | 0 | - |
| Other comorbidities ¶ | 0 | 0 |
| **Desire to conceive** ¶ | 26 (96.3%) | N/A |

* Data shown as mean (SD); SD – standard deviation; ¶ Data shown as N° (%); min- minimal, max- maximal, AS – ankylosing spondylitis; PsA – psoriatic arthritis; BASDAI- Bath Ankylosing Spondilitis Disease Activity Index, TNFi- tumor necrosis factor inhibitors; NSAID – non-steroidal anti-

inflammatory drugs; SSZ – sulfasalazine; MTX – methotrexate; N$^{o}$ – number, $^{\wedge}$ onset of PsA in one mother preconception, $^{\delta}$ -very rare exposure to NSAID(1-2 times/ month), N/A – not available, $^{\S}$ the partners of male patients were monitored 3 times during pregnancy.

**Table 2. Pregnancy and offspring outcomes in patients compared to the general population^**

| Pregnancy evolution and outcome | Cases | General population |
|---|---|---|
| Nº of pregnancies | 33 | 12.142 |
| TTP < 12 months ¶ | 32 (96.9%) | N/A |
| Live births¶<br>Male gender | 30 (91%)<br>13 (43.3%) | 9667 (79.6%)<br>N/A |
| Stillbirths¶ | 0 | 107 (0.9%) |
| Gestational age at delivery (weeks)* | 37.57 ± 1.01 | N/A |
| ≥ 37 weeks ¶ | 24 (80.0%) | 8593 (88.9%) |
| < 37 weeks¶ | 6 (20.0%) | 1074 (11.1%) |
| Type of delivery for live births¶ | | |
| Vaginal | 28 (93.3%) | 9459 (97.8%) |
| Cesarean | 2 (6.6%) | 208 (2.2%) |
| APGAR score | 9.6 ± 0.7 | N/A |
| Weight of live newborn (g)* | 3390.7 ± 342.6 | N/A |
| Weight >2500 g¶ | 30 (100%) | 9566 (98.9%) |
| Small for gestational age¶ | 0 | 101 (1.0%) |
| Spontaneous abortion¶ | 0 | 1135 (9.4%) |
| Elective abortion (weeks 8-9) ¶ | 3 (9.0%) | 1233 (10.2%) |
| Pre-eclampsia/Eclampsia¶ | 0 | 110 (1.1%) |
| Congenital malformations¶ | 0 | 140 (1.4%) |
| Other neonatal diseases that require prolonged stay in neonatal intensive care unit ¶ | 0 | 18 (0.2%) |

*Data shown as mean (SD); SD – standard deviation; ¶ Data shown as Nº (%); Nº – number; N/A – not available, ^ Data from ATLAS platform (surveillance software linking diagnosis, investigations and medication), TTP- time to pregnancy achievement. APGAR score is based on **A**ppearance, **P**ulse, **G**rimace, **A**ctivity, **R**espiration evaluation in the newborn;, stillbirths -*in utero* fetal death after 20 weeks of gestation; spontaneous abortions were defined as clinically recognized pregnancy losses before 20 weeks of gestation ; elective abortions were defined as pregnancies that were terminated on personal request for nonmedical reasons, up to 12 weeks of gestation. Normal weight was defined as >2500g at term. Small for gestational age fetuses were those with a weight below 2 SD adapted for gestational age and sex of the child

**Table 3. Sperm parameters in five patients before and after long term TNFi exposure**

| **Sperm analysis** | **P1** | **P1'** | **P2** | **P2'** | **P3** | **P3'** | **P4** | **P4'** | **P5** | **P5'** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| **Volume (ml)** | 3 | 2 | 3.5 | 2 | 3 | 2 | 1.5 | 3 | 4 | 6 |
| **PH** | 7.5 | 7.5 | 7.8 | 7.4 | 7.8 | 8 | 8 | 8 | 8 | 8 |
| **Liquefaction (min)** | 10 | 10 | 5 | 15 | 10 | 10 | 10 | 20 | 20 | 10 |
| **Agglutination** | - | - | - | - | - | - | - | - | - | - |
| **Concentration ($10^6$/ml)** | 50 | 55 | 45 | 30 | 45 | 65 | 43 | 100 | 66 | 40 |
| **Sperm cell motility (%)** | | | | | | | | | | |
| Rapid progressive | 40 | 50 | 37 | 50 | 50 | 50 | 30 | 30 | 50 | 60 |
| Slow progressive | 20 | 20 | 30 | 0 | 15 | 20 | 35 | 30 | 10 | 0 |
| Non-progressive | 0 | 10 | 0 | 0 | 10 | 10 | 0 | 0 | 15 | 0 |
| Immobile | 40 | 20 | 33 | 50 | 25 | 20 | 35 | 40 | 25 | 40 |
| **Leucocytes** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Morphology** | | | | | | | | | | |
| Normal forms (%) | 65 | 60 | 70 | 60 | 63 | 55 | 53 | 70 | 63 | 50 |
| Atypical forms (%) (head+midpiece+tail) | 35 | 40 | 30 | 40 | 37 | 45 | 47 | 30 | 37 | 50 |
| **Diagnosis*** | N | N | N | N | N | N | N | N | N | N |

P1-5- patient sperm parameters evaluation before TNFi exposure, P1'-5'- patient sperm parameters evaluation after 12 months TNFi exposure, N- normozoospermia, ml- milliliter, min- minutes, PH- logarithmic scale specifying acidity/ basicity of an aqueous solution, agglutination is present (+) or absent (-).

*Diagnosis was based on being within reference values of the World Health organization [18].