Impact of TNF-blocking agents on male sperm characteristics and pregnancy outcomes in fathers exposed to TNF-blocking agents at time of conception

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ABSTRACT

Objective. *Published data were analysed to determine if the use of tumour necrosis factor (TNF) blocking agents in male patients during time of conception is associated with an increased risk of fetal abnormalities or complications during pregnancy. Moreover, we were interested in the impact of TNF-blocking agents on sperm quality characteristics.*

Methods. *We performed a systematic literature review (Medline, online archives of Annual European Congress of Rheumatology and the American College of Rheumatology). One-hundred and thirty-nine Articles of potentially relevant reports were identified and screened for retrieval and nine articles were included in the final analysis.*

Results. *Overall, there were sixty cases, where expectant fathers used TNF-blocking agents shortly before conception. The outcomes of the pregnancies are documented in twenty-eight events. We did not find any documentation of miscarriages or physical abnormities associated with TNF blocking treatment and paternity; however, we did find documentation evidence that sperm motility and vitality even may improve under TNF-blocking therapy. This improvement may be caused by a decrease in disease activity.*

Conclusion. *Published data suggest that TNF-blocking therapy in male patients during time of conception does not increase the risk of adverse pregnancy outcome. In addition TNF-blocking therapy does not appear to reduce male fertility.*

Introduction

TNF-blocking agents have been used for more than ten years for the treatment of a number of inflammatory diseases. These illnesses may occur at any age. Most patients planning pregnancy feel insecure about treatment possibilities as many drugs are contraindicated during pregnancy. There is still limited data for biological treatment used during pregnancy and almost no experience with those drugs in expectant fathers.

Based on recommendations of some respective professional societies and the pharmaceutical industry, biological therapy should be stopped three to six months before pregnancy (1-3). However, discontinuation of treatment may cause a flare of the disease and might also have an influence on sperm characteristics.

The aim of the present study was to analyse published data on the pregnancy outcome in male patients receiving TNF-blocking agents during conception. In addition, we were interested in the impact of TNF blocking agents on sperm quality characteristics.

Methods

We performed a Medline search of the English language literature. The following index key words were used: ("fathering" or "pregnancy" or sperm") and ("Infliximab" or "Adalimumab" or "Etanercept" or "Golimumab" or "Certolizumab").

In addition, we searched the online archive of the Annual European Congress of Rheumatology as well as the American College of Rheumatology. References cited in retrieved articles were also searched for further relevant studies. If a full text and an abstract were available, only the full text was used for analysis. Reviews, commentaries, editorials and letters to the editor (excluding such presenting original data) were not included in the analysis. Our initial search gave 139 studies. After exclusion of non-relevant articles and inclusion of articles not found by the initial search terms, nine entered the analysis.

Results

1. Outcome of pregnancies, when fathers were exposured to TNF-blocking agents

Viktil *et al*. (4) studied twenty-eight patients (twenty-seven with TNF-blocking agents, one with anakinra) who had fathered children during treatment. Unfortunately, no information on the outcomes of the pregnancies was provided.

A study on the effects of TNF blocking agents on sperm characteristics in a total of twenty-six patients with spondyloarthritis reported on three patients receiving TNF-blocking agents who have fathered healthy children (5).

A case series presented in abstract form reported on seven patients who became fathers during therapy with TNF-blocking agents (six with a concomitant therapy with methotrexate) (6). There were six healthy children and one death caused by cordial asphyxia. The authors did not relate this complication to drug exposure.

Paschou *et al*. identified four ankylosing spondylitis (AS) patients, who had fathered six healthy children during treatment with infliximab (7).

In a large case series of pregnancy outcomes in women with rheumatoid arthritis (RA) or Crohn's disease, data were available for the outcomes of ten of the fifteen pregnancies, where the father was exposed to infliximab (8). There were nine live births and one spontaneous miscarriage (in a woman with Addison's disease and a history of previous spontaneous abortion).

La Montagna *et al*. (9) reported on two AS patients who fathered children during infliximab treatment.

Overall, there were 60 cases in which fathers-to-be used TNF-blocking agents. The outcomes of the pregnancies are documented in twenty-eight cases (Table I).

Table I. Outcome of pregnancies with patients fathering children during TNF-treatment.

Study	n. of pregnancies	Documented outcome	Healthy newborns
Villiger *et al*. (2010)	3	3	3
Viktil *et al*. (2009)	27	–	–
Barcelo *et al*. (2009)	7	7*	6
Paschou *et al*. (2007)	6	6	6
La Montagna *et al*. (2005)	2	2	2
Katz *et al*. (2004)	15	10**	9
	60	28	26

*One cordial asphyxia. **One spontaneous miscarriage.

2. Influence of TNF-blocking agents on sperm quality

Suominen *et al*. (10), the only non-human study cited in this manuscript, demonstrated that TNF-α promotes cell survival in the rat seminiferous epithelium and that this effect can be blocked by infliximab.

Mahadevan *et al*. (11) investigated the impact of infliximab on sperm quality in ten patients with Crohn's disease. Comparing pre-infusion and post-infusion semen characteristics, there was a significant increase in semen volume after therapy and a trend toward decreased sperm motility and a reduced number of normal oval forms.

In three AS patients receiving infliximab, La Montagna *et al*. (9) found reduced sperm motility and abnormally shaped sperm. A control group was not included.

Said *et al*. (12) found that spermatozoa exposed to high concentrations of TNF-α resulted in a significant loss of spermatozoa functional and genomic integrity, which can be inhibited by Infliximab.

Villiger *et al* (5) investigated the influence of TNF blocking agents on spermatogenesis in twenty-six spondyloarthritis patients. In ten out of eleven patients without biological treatment sperm abnormalities were found. All eleven patients had poorer sperm motility and vitality than fifteen controls tested during TNF blocking therapy. Sperm quality and morphology were similar in those two groups. There was no significant difference in sperm quality between healthy controls and patients treated with TNF blocking agents.

Discussion

There are very limited data on fathering children while receiving biological therapy. This is in contrast to increased awareness on maternal treatment before and during pregnancy. Most of the national biologics registers record childbearing but do not collect data on the fathers-to-be who are taking a disease-modifying anti-rheumatic drug.

We detected only 60 cases where expectant fathers used TNF-blocking agents during the time of conception. There were no miscarriages or physical abnormities associated with TNF-blocking treatment and paternity.

We identified five studies on the influence of TNF-blocking treatment on spermatogenesis. TNF has a positive influence in the male gonadal tract with an impact on germ cell apoptosis, the control of secretion of peritubular cells and sperm survival. Negative effects on spermatogenesis on high tissue concentrations have also been described (5, 10, 12). In one study, therapy with TNF-blocking agents had a positive effect on sperm motility and vitality, potentially caused by reducing RA disease activity (5). On the contrary, impaired sperm quality was evident in patients without TNF blocking treatment. The authors conclude that TNF blocking therapy does not influence reproduction and recommend that treatment need not be discontinued if fatherhood is planned.

Hardly any national societies give specific recommendations on this topic. The German Society for Rheumatology (1) recommends stopping TNF-blocking agents etanercept and adalimumab for three and infliximab for six months before fathering children. Further prospective studies would be helpful to clarify whether treatment should be discontinued in male patients planning fathering a child. However, particularly due to ethical reasons, it will be unlikely that such trials will ever be performed. Male patients should be informed that according to the information available, therapy with TNF blocking agents does not appear to affect reproduction and pregnancy. Although we have no reported complications of patients who fathered children during TNF-blocking treatment, it should be emphasised that there are only limited data available regarding this sensitive subject.

In conclusion, according to the data published, TNF-blocking agents do not appear to substantially increase the risk of adverse pregnancy outcomes when administered to male patients during the time of conception. Sperm motility and vitality seem to improve under TNF-blocking therapy.

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