The effect of methotrexate on fertility parameters in men with immune mediated diseases

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To determine whether MTX can be quantified in seminal plasma and spermatozoa of MTX-naïve and chronic-MTX users, and to compare the concentration of MTX in seminal fluid and spermatozoa between MTX-naïve users and chronic-MTX users and to evaluate...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sexual function and fertility disorders
Study type	Observational invasive

Summary

ID

NL-OMON55461

Source
ToetsingOnline

Brief title
iFAME-MTX

Condition

- Sexual function and fertility disorders

Synonym
fertility

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ReumaNederland

Intervention

Keyword: fertility, immune mediated inflammatory disease, male, methotrexate

Outcome measures

Primary outcome

* To determine whether methotrexate (solely or as polyglutamate) can be quantified in seminal fluid and spermatozoa of naïve and chronic users.

* To compare the concentration of methotrexate in seminal fluid and spermatozoa between MTX-naïve users and MTX-chronic users.

Secondary outcome

* Determine if there is a statistically significant difference on DNA Fragmentation Index between cases and study-controls.

* Evaluate the associations between MTX concentration (solely or as polyglutamate) in seminal plasma and spermatozoa with those in serum and erythrocytes and with the traditional sperm quality measurements and the DNA Fragmentation Index.

* Determine if there is a time and dose dependent effect on traditional sperm quality measurements and the DNA Fragmentation Index.

* Compare the concentration and the activity of GGH and other enzymes responsible for the intracellular metabolism of MTX in spermatozoa with those found in red and white blood cells.

Study description

Background summary

Methotrexate (MTX) is the cornerstone in the treatment of several immune mediated diseases, such as Inflammatory Arthritis, Psoriasis and Crohn*s Disease. Besides being teratogenic, MTX may also have a negative impact on sperm quality. Recommendations for the use of MTX in men wishing to conceive are inconclusive, mainly because of the lack of studies about the impact of MTX on semen and spermatozoa.

Study objective

To determine whether MTX can be quantified in seminal plasma and spermatozoa of MTX-naïve and chronic-MTX users, and to compare the concentration of MTX in seminal fluid and spermatozoa between MTX-naïve users and chronic-MTX users and to evaluate the effect of MTX concentration on parameters of sperm quality, including the DNA fragmentation index (DFI). In addition, sperm and blood samples from healthy controls will be processed to measure the concentration and enzymatic activity of Gamma-glutamyl hydrolase (GGH) and other enzymes involved in the intracellular metabolism of MTX.

Study design

This study consists of three parts:

Part I has been completed. This was a validation phase. Two validation-control groups were recruited for the validation of the quantification of MTX in blood and in semen.

Part II consists of a case-control study where two different groups of patients and one group of healthy controls will be recruited:

1. MTX-naïve: Twenty five male patients with immune mediated diseases who will start treatment with MTX.
2. Chronic-MTX users: Twenty five male patients with immune mediated diseases who have been under treatment with MTX uninterruptedly for at least 1 year.
3. Healthy controls: Twenty five healthy men.

The MTX concentration in blood, seminal plasma and spermatozoa will be measured before and after MTX exposure in cases from the MTX-naïve group and only after exposure in cases from the chronic-MTX users group. Cases from both groups and study-controls will go through the same andrological evaluation, consisting of a physical examination, medical history, endocrine evaluation, semen quality analysis and DFI.

Part III is the last part of the study. Blood and sperm samples from 10 healthy men will be processed to measure the concentration and the activity of GGH and other enzymes involved in the metabolism of MTX.

All study procedures (incl. signing of the informed consent) except the analysis of the sperm morphology slides and the enzyme measurements, will be performed during 1 study visit for controls, 2 study visits for chronic-MTX cases and during 3 study visits for MTX-naïve cases. These visits will take place at the Erasmus MC. The sperm morphology slides will be assessed at the Radboudumc and the enzymes at the Amsterdam UMC.

Study burden and risks

* Part I of the study (already completed)
Semen validation-controls donated one semen sample obtained by masturbation (in the hospital). Blood validation-controls donated one blood sample (4 ml) during a blood draw for routine usual care (i.e. no extra venapuncture required).

* Part II of the study (participants are currently being included)
- Cases in the MTX-naïve group will visit the hospital 3 times. During the first and second visit (approximately 90 min per visit) one semen sample (obtained by masturbation) and one blood sample (21 ml) will be collected. During these visits MTX-naïve cases will undergo a physical examination and fill in questionnaires. During the third study visit (approximately 30 min) one semen sample will be obtained and a questionnaire about medication use will be filled in.
- Cases in the chronic-MTX users group will visit the hospital 2 times. During the first visit (approximately 90 minutes) one semen sample (obtained by masturbation) and one blood sample (21 ml) will be collected. During this visit chronic-MTX users will undergo a physical examination and fill in questionnaires. During the second study visit (approximately 30 min) one semen sample will be obtained and a questionnaire about medication use will be filled in.
- Study-controls will visit the hospital once (45-60 minutes). During the visit one semen sample and one blood sample (21 ml) will be obtained, a physical examination is performed and the men will fill in questionnaires.

* Part III of the study
Enzyme-controls will visit the hospital once (approximately 30 min). During the visit one semen sample and one blood sample (8 ml) will be obtained.

Participants will not benefit from taking part in this study. The results will provide information about the effects of MTX on male fertility and contribute to a more evidence based advise on stopping or continuing MTX in males who want to conceive.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

SEMEN VALIDATION-CONTROLS
* Males 18 years or older.
* Able to give informed consent.

BLOOD VALIDATION-CONTROLS
* Males 18 years or older.
* Current MTX-users for at least 3 consecutive months.
* Able to give informed consent.

CASES
* Males 18 years or older.
* Diagnosed with an immune mediated disease, such as:
- Rheumatoid Arthritis (RA).
- Undifferentiated arthritis (UA).
- Spondyloarthropathies (SpA):
* Psoriatic Arthritis (PA)

* Ankylosing Spondylitis (AS)
* Reactive Arthritis (ReA)
* Enteropathic Arthritis (EA)
* Undifferentiated Spondylarthropathy (US)
- Juvenile Idiopathic Arthritis (JIA)
- Psoriasis (PsO)
- Eczema (E)
- Crohn*s Disease (CD)
* Methotrexate-naive patients: patients who will start methotrexate therapy (oral and subcutaneous routes of administration are allowed) and who have not received MTX treatment in the 6 months before inclusion.
* Chronic-MTX users: patients who are currently under treatment with MTX uninterruptedly for at least 1 year using a dose equal or higher than 15 mg/week.
* Proven fertility, i.e. the man impregnated a woman (positive pregnancy test) in the past or who
has biological children of his own (Self-report).
* Able to give informed consent.

STUDY-CONTROLS
* Males 18 years or older.
* Proven fertile, i.e. the man impregnated a woman (positive pregnancy test) in the past or who
has biological children of his own (self-report).
* Able to give informed consent.

ENZYME-CONTROLS
* Males 18 years or older.
* Able to give informed consent.

Exclusion criteria

SEMEN VALIDATION-CONTROLS
* Current or past use of Methotrexate.
* Vasectomy.
* Language barrier.

BLOOD VALIDATION-CONTROLS
* Language barrier.

CASES
* Age above 55 years.
* Known infertility (Self-report).
* Current use of Methadone hydrochloride; Nitrofurantoin; Dapsone; Paroxetine; Fluvoxamine maleate; Nifedipine; Colchicine; Cortisone acetate; Dexamethasone;

Methylprednisone; Prednisone (>7,5 mg/day); Sulfasalazine; Triamcinolone hexacetonide; Busulfan; Chlorambucil; Cyclophosphamide; Dabrafenib; Degarelix; Fludarabine; Mercaptopurine; Procarbazine; Triptorelin; Vinblastine; Vinorelbine; Testosterone.
* Current sexually transmitted disease (Self-report).
* Current lower urinary tract infection (Self-report).
* Active infection with Hepatitis B or C virus (Self-report).
* Human immunodeficiency virus (HIV) infection (Self-report).
* Vasectomy.
* Language barrier.

STUDY-CONTROLS
* Age above 55 years.
* Known infertility (Self-report).
* Current or past use of Methotrexate.
* Current use of any medication.
* Current sexually transmitted disease (Self-report).
* Current lower urinary tract infection (Self-report).
* Active infection with Hepatitis B or C virus (Self-report).
* Human immunodeficiency virus (HIV) infection (Self-report).
* Vasectomy.
* Language barrier.

ENZYME-CONTROLS
* Vasectomy.
* Language barrier.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2019
Enrollment:	105
Type:	Actual

Ethics review

Approved WMO Date:	30-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL64218.078.18
Other	NL8674