

# Stop or Go? Relapse prevention training with guided tapering of antidepressants during pregnancy. A pragmatic multicenter RCT to investigate risk and benefits for mother and child.

No registrations found.

<b>Ethical review</b>	Positive opinion
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	-
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON23074

### Source

Nationaal Trial Register

### Brief title

Stop or go?

### Health condition

Pregnant women, depressive symptoms, anxiety, antidepressants, SSRI, tapering of medication

## Sponsors and support

**Primary sponsor:** ErasmusMC

**Source(s) of monetary or material Support:** ZonMW

## Intervention

## Outcome measures

### Primary outcome

Risk (cumulative incidence) of relapse of maternal depressive disorder (as defined by the Structured Clinical Interview for DSM disorders) during pregnancy and up to 3 months postnatal.

### Secondary outcome

Mother:

1. Time to relapse of maternal depressive disorder during pregnancy and up to 3 months after delivery;
2. SSRI use and dosage, psychiatric co-medication (e.g. benzodiazepines), adherence to preventive cognitive therapy;
3. Side effects of (tapering of) medication (checklist);
4. Hazardous behavior (e.g. use of alcohol/drugs or suicidality);
5. Stress, depressive symptoms, anxiety, and childhood trauma;
6. Direct medical costs (until 3 months postpartum), indirect costs (with adjustment for pregnancy leave period), quality of life effects mother;
7. Obstetric complications during pregnancy and delivery (spontaneous abortion, referral midwife to obstetrician, preeclampsia [ISSHP definition], assisted delivery, induced labour for maternal indication [premature, term delivery], epidural anaesthesia for pain, caesarean section).

Child:

1. Specific: child condition at birth (poor neonatal adaptation defined as: 5-min Apgar <7 and/or admission to pediatric ward/NICU);
2. General: gestational age at birth, birth weight, head circumference at birth; these measures also expressed as deviance scores/percentiles;
3. Neuromotor development (General Movements [GM]);
4. Child behavior (Child Behavior Check List at 18 months; parental and caregiver report);

5. Child development as collected from routine data of Centres of Childhood (CJG) up to 24 months after delivery;
6. Direct medical costs, quality of life (proxy).

Other study parameters:

1. Baseline: age, ethnicity, level of education, marital status, parity, unwanted/unplanned pregnancy, Body Mass Index (BMI), somatic conditions (if not exclusion criteria), medication use and substance use (smoking, alcohol, drug);
2. Maternal (epi)genetic and pharmacogenetic markers: e.g. 5HTTLPR, BDNF, FKBP5, TREK1, COMT, CRH1, CYP2D6 and CRHBP) (Kupfer, 2012)<sup>40</sup>;
3. Child (epi)genetic markers: e.g. NR3C1, HTR2A;
4. Maternal hair cortisol will be used as a validated biomarker for maternal and child cortisol exposure during pregnancy;
5. To measure the chronic exposition to SSRIs, meconium will be collected. SSRIs in meconium are measured by a validated method according to LCH guidelines on LC-MS/MS<sup>41</sup>;
6. Breast milk will be collected from women breastfeeding their baby, to measure SSRI concentration;
7. If possible, placenta and cord blood will be collected for further investigation (measurements of SSRI levels in cord blood).

## Study description

### Background summary

Rationale:

About 2% women in the Netherlands use Selective Serotonin Reuptake Inhibitors (SSRIs) during their pregnancy for symptoms of depression and/or anxiety. SSRI use in pregnancy is controversial. On the one hand SSRIs may be toxic to the intrauterine developing child, while on the other hand, relapse of depression and/or anxiety during pregnancy holds risks for both mother and child. Among patients and professionals there is an urgent need for evidence from randomized studies to make rational decisions regarding continuation or tapering of SSRIs during pregnancy. No such studies exist to date.

## Objective:

The aim of this study is to investigate the effect of preventive cognitive therapy with guided tapering of SSRIs in early pregnancy as compared to continuation of SSRIs during pregnancy. We will study effects on both mother and child with a pragmatic approach.

## Our hypotheses are:

- 1) Tapering of SSRIs with added preventive cognitive therapy (CT) increases the risk of clinically relevant maternal relapse of depression in excess of [absolute] 15% compared to continuation of SSRIs. If rejected, then discontinuation is deemed non-inferior with regard to relapse risk;
- 2) Tapering of SSRIs is better than continuation of SSRIs with respect to child development;
- 3) Assuming no relevant effects of discontinuation on the mother and no effects on the child, discontinuation decreases total costs per woman and child on a 3 months and projected long term base.

In absence of clinical differences between the two options, tapering of SSRIs will be declared preferential during pregnancy.

## Study design:

A nationwide pragmatic multi-center randomized controlled non-inferiority trial (RCT).

## Study population:

The study population consists of 200 women who are between 8-16 weeks pregnant and use SSRIs without clinically relevant depressive symptoms.

## Intervention:

After informed consent, women will be randomly allocated into two groups:

1. Preventive cognitive therapy with gradual, guided discontinuation of SSRI under clinical management (intervention group);
2. Continuation of SSRI (control group).

Main study parameters/endpoints:

Primary outcome:

Risk (cumulative incidence) of relapse of maternal depressive disorder (as defined by the Structured Clinical Interview for DSM disorders) during pregnancy and up to 3 months postnatal.

Secondary outcomes:

1. Child condition at birth (Apgar, gestational age, birth weight, head circumference);
2. Child neurodevelopmental outcome at 3 months (General Movements);
3. Child behaviour (CBCL) at 18 months;
4. Cost effectiveness (including indicated second echelon care, hospital delivery and clinical child observation in case of SSRI use).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

All participants in the study receive regular check up on the potential return of their depressive symptoms. The main risk in this study involves the tapering of medication in women who are mentally stable. Although tapering of antidepressant medication in mentally stable patients is part of evidence based clinical practice, it could introduce relapse of previous depressive symptoms. We realize that in pregnant women this involves risks for the mother and her unborn child. Therefore, each patient will be critically evaluated by an experienced psychiatrist/clinical psychologist at inclusion, to judge whether it is clinically justified to taper antidepressant medication. If so, antidepressants will be tapered with close monitoring by a general practitioner or psychiatrist, and additional preventive CT will be provided. The provision of preventive CT in addition to tapering medication is in accordance with (inter)national guidelines (Multidisciplinary Dutch guidelines 2013, APA 2010, NICE 2009)<sup>1,2,3</sup>.

Of note is that in both randomized groups concomitant therapy is allowed in this pragmatic trial, e.g. the administration of benzodiazepines.

Additional burdens without risks will be:

1. Blood sampling of the woman at inclusion;
2. A structured psychiatric interview of the woman at inclusion (30-90 minutes) and at 12 weeks after delivery (+/- 30 minutes);

3. Questionnaires at fixed time points: inclusion, 24 and 36 weeks pregnancy, 4 and 12 weeks and 18 months after delivery (+/- 30 minutes);
4. Collection of meconium of the newborn by the parents;
5. Collection of breast milk when breastfeeding;
6. Collection of placenta and cord blood (if possible);
7. Collection of hair (+/- 1 cm<sup>2</sup>) and a buccal swab at 3 months after delivery of both mother and child;
8. The child born from the included woman will be videotaped in a non-invasive home observation at 3 months of age (30-60 minutes) to measure general movements of the child. The mother is allowed to be present during the assessment.

A potential benefit of participating in this study might be the superiority of the intervention (i.e. tapering of SSRI with additional preventive CT) compared to treatment as usual with respect to maternal and child health outcome. The study guarantees access to preventive CT therapists without additional costs and waiting lists for participants who are allocated to the intervention arm.

### **Study objective**

- 1) Tapering of SSRIs with added preventive cognitive therapy (CT) increases the risk of clinically relevant maternal relapse of depression in excess of [absolute] 15% compared to continuation of SSRIs. If rejected, then discontinuation is deemed non-inferior with regard to relapse risk.
- 2) Tapering of SSRIs is better than continuation of SSRIs with respect to child development.
- 3) Assuming no relevant effects of discontinuation on the mother and no effects on the child, discontinuation decreases total costs per woman and child on a 3 months and projected long term base.

In absence of clinical differences between the two options, tapering of SSRIs will be declared preferential during pregnancy.

### **Study design**

T0: Inclusion: SCID, HAM-D, Mind2Care, STAI, EPDS, PSS, TIC-P, EQ-5D-5L, bloodsample;

T1: 24 weeks: CTQ, EPDS, STAI 6-item, PSS, EQ-5D-5L;

T2: 36 weeks: HAM-D, EPDS, PSS, STAI 6-item, TIC-P, EQ-5D-5L;

T3: Delivery: registered details;

T4: 4 weeks after delivery: EPDS, PSS, STAI 6-item, TIC-P, EQ-5D-5L;

T5: 12 weeks after delivery: SCID, HAM-D, EPDS, PSS, STAI 6-item, TIC-P, EQ-5D-5L, GM, hair cortisol;

T6: 18 months after delivery: CBCL, C-TRF, LDS;

T7: 24 months after delivery: information of the CJG.

## **Intervention**

After informed consent, women will be randomly allocated into two groups:

- 1) Preventive cognitive therapy with gradual, guided discontinuation of SSRI under clinical management (intervention group);
- 2) Continuation of SSRI (control group).

## **Contacts**

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## Eligibility criteria

### Inclusion criteria

1. Less than 16 weeks pregnant;
2. SSRI use for depressive disorder.

### Exclusion criteria

1. Insufficient proficiency in Dutch or English;
2. Multiple pregnancies (because of increased risk for adverse birth outcomes that might confound statistical analyses);
3. Severe medical conditions that involve treatment decisions overriding research participation;
4. Current relapse of depression after previous attempts to taper SSRIs;
5. Current other psychiatric disorders (i.e. psychosis, bipolar disorder, severe obsessive-compulsive disorder, substance abuse, suicidality and/or serious self-harm).

## Study design

### Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active

### Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	01-01-2015



Enrollment: 200  
Type: Actual

## Ethics review

Positive opinion  
Date: 16-07-2014  
Application type: First submission

## 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
NTR-new	NL4551
NTR-old	NTR4694
Other	2014-003086-25 : EudraCT

## Study results