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ABSTRACT

Introduction

Ten percent of all pregnant women are depressed. Standard management of pregnant women with moderate depression is treatment with Selective Serotonin Reuptake Inhibitors (SSRI). Previous observational studies on neurodevelopment after fetal SSRI exposure show conflicting results. Our primary objective is to compare the cognitive development in children exposed to sertraline and maternal depression with those exposed to maternal depression and

placebo in fetal life. Our hypothesis is that there are no significant neurodevelopmental differences between the groups. As a secondary objective we will study the add-on effect of sertraline to Internet-based Cognitive Behaviour Therapy (ICBT) in treatment of moderate depression during pregnancy.

Methods and analysis

MAGDALENA is a randomised, placebo-controlled, double-blinded trial in the Stockholm Healthcare region with 2.3 million inhabitants. The women are recruited in week 9-21 of pregnancy either through Antenatal Health Clinics or through social media. They are to be diagnosed with moderate depression and have no ongoing antidepressive therapy or any serious comorbidity to be included. The women in the intervention arm receive sertraline combined with a twelve-week period of ICBT, whereas the control arm is treated with placebo and ICBT. Our primary outcome is the cognitive development in the offspring at the age of 2, assessed with Bayley Scales of Infant and Toddler Development®, 3rd edition (BSID-III®). We aim at recruiting 200 women, 100 women in each treatment arm, to ensure statistical power to detect a clinically relevant difference between the groups.

Ethics and dissemination

This randomised trial will provide long sought evidence about the effects of SSRI and maternal depression during pregnancy on the neurodevelopment in the offspring. Full ethical approvals have been obtained. Results will be disseminated at scientific conferences, published in peer-reviewed journals, and made available to the public in different ways including social media.

Key Words: Antenatal depression, Drug metabolism, Infant, Internet-based Cognitive behaviour therapy, Neurodevelopment, Pregnancy, Randomised controlled trial, Serotonin Reuptake Inhibitors,

Article Summary

Strengths and limitations of this study

+ To our knowledge, this is the first randomised trial to separate the neurodevelopmental effects of fetal SSRI exposure from the possible effects from the underlying maternal depression.

+ The study will provide evidence for the add-on effect of SSRIs to ICBT for treatment of moderate depression during pregnancy.

- We may risk a limited generalizability of our findings due to strict inclusion and exclusion criteria.

- There is a risk for loss to follow-up due to our long follow-up period. This risk would be similar between groups because of our randomised design.

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Introduction

Background

Although approximately ten percent of pregnant women are depressed, the prescription-rate of antidepressants decreases during pregnancy as compared to the preceding months [1,2,3] Untreated prenatal depression is associated with pregnancy complications such as preeclampsia[4], low birth weight and prematurity[5] and increased plasma levels of stress hormones in the pregnant woman and the neonate.[6,7] Currently, 2,4% of pregnant women in Sweden and 6% of the ones in USA are treated with SSRIs.[8,9] Increased risk for SSRI-related birth-defects has not been reported for most SSRIs except that fluoxetine and paroxetine seem to be associated with a small increase in the risk for heart defects.[10]

The question if fetal SSRI exposure causes long-term neurodevelopmental effects remains unanswered.[11] Observational studies have reported a twofold increased risk for autism spectrum disorder (ASD),[12-15] but recently two large register studies explained this increase by confounding factors, emphasizing the role of genetic and social factors as opposed to drug exposure alone.[16,17] A recent review also concluded, that the increase was not significant when comparing to women with previous affective disease or in sibling studies.[18] To our knowledge, there is no previous randomised controlled trial in this field.

Our main objective is to clarify the cognitive effects on the children by pursuing a randomised, controlled, double blind study. We compare the cognitive development at two years of age in children to women with moderate depression during pregnancy, treated with either Internet-based Cognitive Behaviour therapy (ICBT) and sertraline (a SSRI compound) or ICBT and placebo. The Swedish acronym of the study, MAGDALENA, reflects this main objective: *"Maternal Affective Disease during Pregnancy: Depression and Antidepressant Drugs and Effects on the Neurological Development and Adaptation"*.

Our secondary objective is to understand the add-on effect of sertraline to Internet-based Cognitive Behaviour Therapy (ICBT), a web-based self-treatment program with active therapist support over the internet. ICBT is a well-documented treatment for depression used in regular psychiatric care.[19] It has been shown that pregnant women feel that psychotherapy needs to take the special case of being pregnant into account to be credible and engaging.[20] Postpartum depression has been targeted in online trials[20-23], but not antenatal depression. Because of this, we developed an ICBT program to be useful for treatment of antenatal depression based on the ICBT for depression used at our Internet Psychiatry Clinic. The modified ICBT was tested in a pilot RCT with good results. The effect size compared to regular maternity care was of clinical importance and significant, (Hedges g=1.21, p<.001)[24] The Swedish guidelines state that mild and moderate depression should primarily be treated

with psychotherapy or antidepressants. Cognitive behaviour therapy and interpersonal therapy are recommended as the first choice of therapy. Severe depression should be treated with antidepressants or electroconvulsive therapy (ECT). The recommendation does not give guidance on the value of combination therapies for any level of depression.[25] Combination therapy with CBT and antidepressants appear more effective than antidepressant therapy alone in treatment of major depression,[26] but this has not been studied in pregnant women. Given the *in-utero* effects of untreated depression during pregnancy,[7] it might be rational with a dual treatment to achieve prompt symptom reduction. The effects of ICBT are comparable to the effects seen with traditional CBT, hence having the potential to be a cost-effective and accessible treatment alternative.[19,24,27,28] Our large group of patients and unique design with and without sertraline treatment allows us also to pursue exploratory tertiary studies in the pregnant women and in the newborns.[29,30]

Objectives

Primary and secondary objectives

Our primary objective is to study cognitive development at 2 years of age in children prenatally exposed to moderate maternal depression treated either with sertraline and ICBT (Intervention) or with ICBT and placebo (Control). Our hypothesis is that there is no significant neurodevelopmental differences between 2 year old children exposed to the intervention treatment as compared to the control treatment, measured with established scoring methods.

Our secondary objective is to evaluate the add-on effect of treatment with sertraline to an ICBT-program for antenatal depression. Our hypothesis is that sertraline provides a significant add-on effect to ICBT-therapy.

Exploratory tertiary objectives

The large material and unique design with one SSRI-exposed and one placebo-treated arm allows exploratory studies on tertiary aspects related to physiological and adaptive changes in depressed pregnant women and in their newborns. We will study the risk of preeclampsia, bleeding and caesarean section and potential changes of biochemical parameters and hormones during the course of pregnancy in the two study groups.[4,31-33] Paediatric exploratory objectives include clarification of type and prevalence of signs and symptoms of neonatal maladaptation and risk of admission to a neonatal care unit. The design allows a subgroup study of maternal-fetal attachment and bonding style differences between the groups.[34]

We will explore interindividual variation in sertraline pharmacokinetics during and after pregnancy and in newborns and how it might relate to different genetic variants of drug metabolizing enzymes in pregnant women and newborns.[35-37] Likewise we will explore the epigenetic differences between the groups in mothers and newborns.[38]

Methods and analysis

Trial design and setting

The MAGDALENA Study is a prospective, randomised, placebo controlled, double blinded, single centred, clinical investigation of pregnant women with moderate depression recruited from the Stockholm catchment area (2.2 million inhabitants and 28000 deliveries annually) with multiple delivery units. The study group receives sertraline (or placebo) clinically titrated to a maximum daily dose of 150 mg. The study and control groups are both treated with ICBT.[24] The trial design includes two different recruitment pathways (A and B) (Figure 1). The primary outcome is achieved with scoring of the neurodevelopment of the child at 2 years of age. The framework for neurodevelopment is non-inferiority, whereas the add-on effect of SSRI to ICBT is a traditional superiority test. The tertiary objectives are exploratory.

Figure 1. Trial design and participant timeline for the two recruitment pathways. The figure also shows the treatment with placebo/sertraline from visit 2 (pregnancy week 13-24) to visit 6 (4 weeks postpartum) and the ICBT for both groups for 12 weeks, between visit 2 and visit 4 (pregnancy week 26-36) and monitoring of therapy for the two groups. The post-partum follow-up of both mother and child are shown. The different scales and examinations are, as presented in the figure: 1) Edinburgh Postnatal Depression Scale (EPDS)[39], 2) The diagnose moderate depression is confirmed according to clinical standard evaluation. Inclusion and exclusion criteria presented in table 1. 3) Evaluation with Montgomery-Åsberg Depression Scale (MADRS)[40], 4) Modified Finnegan Neonatal Abstinence Scale (NAS)[41], 5) Hammersmith Neonatal Neurological Examination (HNNE)[42], 6) Hammersmith Infant Neurological Examination (HINE)[43], 7) Bayley Scales of Infant and Toddler Development III® (BSID III®)[44].

Recruitment and blinding

Pregnant women are recruited either from the antenatal health clinics (Figure 1, Pathway A) or through social media and our study website www.magdalenastudien.se (Figure 1, Pathway B). Pregnant women visit their midwives at the antenatal clinics, commonly with their partners, around ten times during pregnancy free of charge. In pathway A, the midwives inform about the study at a regular visit. The recruitment through the study website, pathway B, is simplified by informing about the study to potential subjects continuously through social media, pregnancy related information platforms, different blogs and podcasts. Smartphone pregnancy applications are popular, reaching about 75% of pregnant women in cross-sectional studies in English and Spanish speaking countries. We assume similar, if not higher, usage in Sweden.[45,46] In both pathways, the women are directed our study platform at the internet psychiatry website, www.internetpsykiatri.se. They are asked to fill the Edinburgh Postnatal Depression Scale (EPDS)[39] self-test to assess the degree of depressive symptoms as well as to sign the first informed consent form. Regardless of recruitment pathway, the women will continue their regular visits at their home antenatal clinic.

We have chosen 13 or more points on the EPDS for further evaluation of eligibility for the study. The reason is that it has been found to be the optimal cut-off point with 77% sensitivity and 94% specificity for detection of depressive symptoms during pregnancy.[39] The subjects scoring 13 points or more on the EPDS self-test and lacking exclusion criteria are scheduled to meet one of our three study psychiatrists for clinical evaluation, including SCID-I directed

interview (Structured Clinical Interview for DSM IV axis I disorders)[47], review of eligibility criteria and signing of the final informed consent form. (Visit 1, Fig.1, Table 1). The included women are allocated to the next consecutive patient number and randomised to treatment by Karolinska Trial Alliance (KTA), see below. The KTA will also ensure correct blinding for all trial participants, care providers, outcome assessors and data analysists, including labelling of the study drug packages. The drug treatment with study drug (sertraline or placebo) is initiated after visit 2 (Fig.1). At the same time, the women start ICBT treatment using the internet psychiatry website.[19,24] Both study and control groups receive capsules of identical appearance and packing (See below). The treatment code is broken and a new clinical evaluation is performed by the study psychiatrist one month after the delivery. The treatment will be continued for one year after the delivery for all patients in the active treatment arm. The women in the placebo group that haven't reached remission will also be offered treatment with SSRI. Both the women and the psychiatrist are forbidden to inform anyone in the study about which group they have belonged to, to ensure the continued blinding of the study. This is particularly important regarding the paediatricians and paediatric psychologists assessing the children.

Inclusion Criteria	▪ Age >18 years ▪ Pregnant in week 9 to 21 after last menstrual period. ▪ Verified moderate depression according to SCID-I (with or without a concomitant anxiety disorder) and a clinical evaluation. ▪ Ability to use the internet platform for ICBT in Swedish as assessed by the study midwife. ▪ Reported ability to participate in all study visits for mother and child.
Exclusion Criteria	▪ Reported abuse of alcohol or drugs ▪ Reported serious psychiatric disorder[1] ▪ Known allergy or idiosyncratic reaction to sertraline ▪ Ongoing medication with antidepressants, mood-stabilizers, central stimulants, antiepileptic drugs, opiates, insulin, oral anti-diabetics, antiarrhythmics or steroids. ▪ A severe somatic disease[2] that requires medical treatment. A high suicidal risk during screening or when included into the study. These women will be excluded from the study and actively transferred to necessary psychiatric care.

Table 1. Inclusion and exclusion criteria for the MAGDALENA study. [1)] Psychosis, bipolar disorder, severe melancholic or psychotic depression, severe personality disorder, autism, ADHD/ADD with ongoing drug treatment or mental retardation [2)] Severe heart and lung disease, kidney disease, liver disease, diabetes mellitus, epilepsy with drug treatment and any severe somatic disease that requires regular treatment with systemic steroids.

Figure 2. The recruitment base in Stockholm Healthcare Region. Numbers based on an analysis of prescription of SSRI:s in pregnant women in years 2013-2016 in the Stockholm healthcare region with 2,3 million inhabitants Acknowledgements).

The study drugs

The investigational medicinal product (IMP) is a capsule containing either sertraline hydrochloride or placebo manufactured by APL (Apoteket Produktion & Laboratorier AB, Stockholm, Sweden). The capsules of active drug are made of hard gelatine and filled with sertraline hydrochloride corresponding to 25mg sertraline using Zoloft® (25mg sertraline film-coated tablets, Pfizer Ltd, New York) and with a microcrystalline cellulose filler. The placebo capsules are made of identical microcrystalline cellulose filler embedded into an identical hard gelatine capsule. The IMP is delivered by the producer in sealed HD polyethylene containers, labelled according to a randomisation list. Patients are randomised to treatment by Karolinska Trial Alliance (KTA) with block randomisation. The size of these blocks is blinded for the investigators.

The treatment with sertraline (or placebo) starts with titration of a dose of 1 capsule (25 mg sertraline or placebo) once daily for 5 days, after which the dose is increased to 2 capsules (50 mg of sertraline or placebo) once daily until the first treatment evaluation (Visit 3, Fig.1). At visit 3 the daily dose can be increased to 4 capsules (100 mg of sertraline or placebo) once daily if clinically indicated, with titration of 3 capsules (75 mg of sertraline or placebo) once daily for 5 days. At visit 4 after 13 weeks of treatment, the dose can be increased further to a maximum 150 mg daily, without titration, if clinically needed. The decision of need to increase drug dosages is based on MADRS scores and a clinical evaluation made by the study psychiatrist. To follow and increase the adherence to treatment, the women will get a limited amount of capsules at each visit, motivating them to return for the next visit and giving the study midwife a way to notice if the subject is not taking the drug. Additional telephone contacts with the psychiatry nurse are performed if concerns about the treatment effect are raised, and an additional visit to the psychiatrist is scheduled if necessary.

The Internet-based Cognitive Behaviour therapy

The ICBT-treatment is 12 weeks long and guided by a psychologist who is available online. It consists of an online platform where patients log in to answer questionnaires and work with self-help material covering the core materials in CBT for depression including interactive worksheets and exercises. They are also assigned weekly homework to report to their personal therapist. A direct messaging system allows for asynchronous correspondence with one of the therapists at any time and get a reply within a day or two. The platform allows monitoring to what extent the patients adhere to the therapeutic sessions.

The pregnancy-related adaptations to the treatment consist of an extra module on pregnancy related symptoms that can lower mood at the beginning of the treatment and an extra module on relationships at the end of treatment. Other than that, the interventions mostly mirror those described and used by us in our ICBT-platform for non-pregnant adults.[19] The examples and cases includes concern pregnant women and their thoughts on pregnancy and becoming a parent and expanding their family. The core methods of the treatment are behavioural activation (increasing positive and valued activities) and cognitive restructuring (challenging own thoughts and distance oneself from dysfunctional thoughts and rumination).

Outcome measurements

Primary outcome: effect on neurodevelopment at 2 years of age

The cognitive development at 2 years of age is the primary outcome. The outcome in children exposed and not exposed to sertraline *in utero* is measured with the standardized Bayley Scales of Infant and Toddler Development III (BSID-III®)[44] and compared between the groups. The BSID-III consists of the Cognitive, Language and Motor Scales that are performed by a child psychologist, and the Social Emotional and the Adaptive Scales that are parental questionnaires. The Cognitive and Language scales have proven to be good predictors of preschool mental test performance.[48] These scales are largely used in screening for cognitive developmental delays,[49] and have been used in studies of cognitive development after intrauterine drug exposure.[50-52] Results from the subscales will be converted to composite scores with a median of 100 and a standard deviation of 15. For each subscale, a composite score of <85 (<-1SD) will be considered abnormal. A difference of 7 points (0.5 SD) between the groups will be considered significant, which is in line with the assumptions made in previous similar studies.[49]

Sample size calculation

A difference of 7 points (SD 0.5) with a power of 80% (α: 0,05) in the results when testing with BSID-III® at 2 years of age is estimated to give a clinically important significant difference in a sample of 73 participating children in each group. Therefore we aim at recruiting 100 mothers in each group.

Secondary outcome

The main psychiatric secondary outcome is the add-on effect of sertraline to the treatment with I-CBT on depressive symptoms measured with MADRS-S (Montgomery-Åsberg Depression Rating Scale, Self-Report)[53] which is performed weekly throughout the 12 week treatment period.

Sample size calculation for the secondary outcome

The additional effect of sertraline as compared to standard ICBT plus placebo will be evaluated by comparing effects on MADRS-S scores between the groups. Data on the total effect of CBT combined with antidepressant therapy is limited. The standardized effect of psychotherapy can be as high as 0.74 when compared to placebo and 0.38 when compared to face-to-face psychotherapy.[26] ICBT is largely self-directed even with therapist guidance, which is likely to put a higher demand on the patients in terms of initiative and maintaining the motivation compared to face-to-face-treatment. Therefore, it is likely that the added effect of SSRI will be larger than what has been found in face-to-face CBT, though not as large as when compared to placebo alone. We therefore hypothesize a standardized effect size of d=0.50 (Cohen). This is also the minimal added effect that we would consider clinically relevant considering the possibility of negative side effects and the documented efficacy of ICBT alone.[24] A sample size calculation with standardized effect equal to 0.5 (Cohen), alfa-value=0.05 and power 80% requires 64 persons in each group. Therefore to recruit 100 patients in each group will fulfil the power calculation.

Exploratory tertiary studies

Exploratory maternal outcomes include the effects on levels on prolactine and cytokines and the risk for postpartum bleeding measured in mL and postpartum anaemia measured with haemoglobin day 2 for the SSRI-exposed women as compared to the placebo-exposed. We also evaluate the risk of preeclampsia, placental abruption and increased caesarean section rate.

The neonatal exploratory outcomes include admission to neonatal care, neurological evaluation with Hammersmith Neonatal Neurological Examination (HNNE)[42] and modified Finnegan Neonatal Abstinence Scales (NAS)[41] and measurement of glucose and concentrations of sertraline in plasma.

In a sub-cohort, blood samples from the umbilical cord and placental biopsies are taken to study eoigenetic effects (DNA methylation, genome width, gene and miRNA expression) between SSRI-exposed and the non-exposed within this cohort.

We will study differences in maternal-child bonding/attachment during and after birth and also breastfeeding occurrence. Prenatal Attachment Inventory-Revised questionnaires and video recordings analysed by "Dr Feldman's micro-coded behaviours" will be used which is a valid tool to study attachment.[54] A comparison will be made between the two groups.

The pharmacokinetic analyses include studies of interindividual variability in plasma sertraline concentrations and its change during the course of pregnancy and postpartum (mean concentration/(dose in mg/kg) with confidence intervals. Pharmacogenetic variants of drug metabolizing enzymes and transporters will be studied in pregnant women and newborns. Umbilical cord blood and venous blood from the neonate will be taken and plasma sertraline levels are assayed. Variability in exposure to sertraline between the neonates will be investigated and the levels will be related to the degree of maladaptation syndrome.

Data management

Each subject will receive a study number for identification. Data will be collected continuously and entered into the electronic Case Report File (eCRF) within two weeks from collection. The e-CRF includes range checks for data values to promote data quality. For the study database we are using an electronic system, Pheedit version 3,0; SAS Institute Inc., Cary, NC, provided by Stockholm Healthcare Region, Sweden. The data is encrypted and safely stored on an electronic server at the Karolinska Institute in Stockholm. The e-CRF is previously used in randomised controlled studies.[55] After completed data collection, the investigators will receive unidentified patient data withdrawn from the CRF and synchronized with data from the internet psychiatry platform. The internet psychiatry platform was also used in our previous study.[24] The investigators will analyse this data for the different endpoints of the study. The samples from whole blood (mainly to extract DNA for pharmacogenetic analyses in the mother and in the newborns), plasma, cord blood, placenta biopsies and the buccal swabs will be stored in the biobank at Karolinska Institutet in Stockholm, available for analyses and future research.

Statistical Methods

The main analyses will be done according to the intention to treat principle. Data will also be analysed per protocol to achieve an efficacy analysis. The primary endpoint, results of BSID III® will be analysed with Student's T-test. Multiple imputation will be used for missing data. The variables used in the imputation mode will be smoking, education level and parity. All patients' demographic data will be analysed by descriptive (mean, median and range)

statistics. Fishers exact test will be used for dichotomous variables such as infant sex, mother's smoking and optimal/suboptimal neurology at Hammersmith neonatal neurological examination. Throughout the analysis, the mean and standard deviation will be calculated for all continuous data using Student's T-test. The non-normally distributed continuous variables, including the results from Hammersmith neurological scales will be analysed with the Mann-Whitney u test and the results of MADRS-S by Cohens effect size. For categorical variables, absolute frequency, percentages and/or proportions are calculated and Fishers exact test will be used. The treatment effect analysis will be a multilevel model for longitudinal data with timepoints nested within individuals (a.k.a. Growth Curve Modeling) using MADRS-S scores from baseline, each of the 12 weeks in treatment, and post treatment. A p-value of <0,05 will be considered significant. Sub group analyses will be performed for smokers, parity, maternal age and education level. Spearman's correlation test will be used to test the correlation between maternal and infant drug concentration.

Ethics and dissemination

Adverse events

Sertraline is one of the recommended drugs for depression during pregnancy in Stockholm Healthcare Region by the Drug and Therapeutics Committee with high adherence.[56,57] Sertraline is also one of the most prescribed SSRIs in the Nordic countries, and is widely used across Europe for treatment of depression during pregnancy.[3,58,59] Thereby the therapeutic profile, the adverse effects and the adverse reactions are well known to the study psychiatrists.

An adverse event (AE) is defined as any undesirable experience associated with the use of the trial drug, sertraline or placebo. A serious adverse event (SAE) is defined as death, a life-threatening event, hospitalization (initial or prolonged), disability, permanent damage or a congenital birth defect. Expected serious adverse reactions are listed in the Summary of Product Characteristics (SPC). A Suspected Unexpected Serious Adverse Reaction(SUSAR) is defined as an adverse effect not listed in the SpC and not mentioned in the SPC as anticipated due to pharmacokinetic properties of the drug, or as a reaction that has occurred with other drugs in this class, but not with the study drug. Unexpected adverse events to ICBT will also be reported. All adverse events occurring after enrolment are documented in the electronic Case Report Form (e-CRF). The adverse events will be reported to the principal investigator, who will report to the sponsor, and in due cases the Karolinska Trial Alliance (KTA) for registration in EduraVigilance. All unexpected serious adverse reactions have to be reported within 24 hours after notification by the study personnel. In case of a serious adverse event such as death or a life threatening event, the PI will raise the issue of breaking the code and termination of the study with the Data Monitoring and Safety Committee (see below). The committee are responsible for the final decision of study termination. The sponsor will each year of the study perform a safety report (DSUR) to Swedish Medical Products Agency.

Monitoring and Study safety

An independent monitor from Karolinska Trial Alliance (KTA), Karolinska University Hospital, will continuously control that the study follows approved protocol, with regular audits with the study midwife and the PI. The staff at KTA have all relevant certifications for Good Clinical Practice (GCP) procedures. Participation in the study is voluntary and women are free to discontinue their participation at any time and for whatever reason without explanations. Midwives at the outpatient clinics and at the delivery clinic have been made aware of this. A Data Monitoring and Safety Committee (DMC) with senior experts in biostatistics, psychiatry, clinical pharmacology (sub-specialised in paediatrics) and neonatology. The committee can at any time if there is any suspicion of a serious adverse event break the code and undertake necessary precautions including stopping the study. The committee is independent from the sponsor with no competing interests or involvement in the design, planning or management of the study. The DMC is also responsible for developing guidelines for interruption of the study and for any interim analyses. The DMC is responsible for deciding if sub-study exploratory investigations can be carried out before the recruitment of all 200 mothers and all 2-year neurodevelopment investigations are completed.

Dissemination plan

This study has as main aim to clarify if any long-term effect on neurodevelopment can be detected in children exposed to sertraline therapy *in utero*. Other issues will be studied as secondary and tertiary objectives including evaluation of the add-on effect of sertraline to ICBT in moderately depressed pregnant women. The study team will design and implement a knowledge translation (KT) plan using established methods for dissemination of scientific results but also modern communication strategies using social media. The KT plan will benefit from strength of being a multidisciplinary scientific group with access to numerous regional, national and international scientific and clinical communities and active involvement of many of the study group scientists in communication with patient groups on psychiatric health and drug therapy during pregnancy. The team has combined years of experience to communicate with colleagues on drug recommendations and achieve high adherence to them using a combination of multifaceted (marketing, continuous medical education, decision support and quality network with colleagues).[56,57] In summary we will use established scientific channels to communicate our findings (A): 1. At national and international scientific meetings, 2. As international scientific publications including publishing our study protocol and 3. By contacting relevant international bodies for development of guidelines on best practice in treatment of psychiatric diseases during pregnancy including WHO. We will also use modern communication methods[56,57] (B): 1. To summarize our findings for laymen and pregnant groups in Swedish and English and 2. To cooperate with these groups to have information disseminated through their publications and websites. Our aim is to improve knowledge about the need to a higher degree treat depression during pregnancy with the alternatives that we and others have found effective. If we, as hypothesized, will find no effect of sertraline therapy on neurodevelopment in two year old infants, it will be one of the most relevant findings to communicate scientifically and to laymen. The legitimacy of our findings will be high if the results are published in peer-reviewed journals and presented at national and international scientific conferences for scrutiny and discussion.

Discussion

We hypothesise that sertraline exposure in therapeutic dosage during pregnancy does not affect the cognition in the offspring as assessed by BSID-III® at 2 years of age. Recent large register based studies[16,17] support our hypothesis and imply the importance of a randomised controlled trial to receive sound evidence in this question. As the previous observational studies comment,[12,13] they have not found a way to adequately adjust for unmeasurable confounders, such as genetic inheritance and disease severity, that we suspect play a significant role when interpreting the results. Using a randomised design in the MAGDALENA study, we minimize the risk for confounding factors.

We also aim to clarify whether combination therapy with ICBT and sertraline is an adequate treatment alternative for moderate depression during pregnancy. This new treatment option provides the pregnant women relevant pregnancy-related questions and the possibility to individually schedule the treatment sessions. Also to our knowledge, no prior placebo-controlled clinical trials have assessed whether combination treatment is superior to treatment with ICBT alone, which we are doing. The risks for the participating women and their offspring are not increased compared to the regular treatment available, as sertraline is widely used in clinical routine in Sweden today. On the contrary, the participating women will have a more thorough follow up than in clinical practice.

The ethics of performing a RCT in this field has been discussed.[60,61] Our study design with ICBT and sertralin or placebo for depression during pregnancy was enabled by recent studies that confirmed the safety and efficacy of ICBT in treating depression, including prenatal depression.[24,28] To date, there is to our knowledge no other study group performing a similar study with the neurodevelopment of the offspring as the main outcome measure. An ongoing Dutch study group randomise clinically undepressed women on antidepressive treatment to either guided drug discontinuation with CBT or continuation of drug therapy.[62] Their primary outcome is the incidence of relapse or recurrence of maternal depression, but they also look at the long-term neurodevelopment with questionnaire based follow-up at 18 months. We consider our method with psychological assessment at 2 years of age more reliable than parental questionnaires. We think that these two studies will complement each other well. Our study will have the unique opportunity to distinguish the effects of exposure to SSRI in utero from the ones of underlying depression, considering our inclusion criteria of moderately depressed women.

A limitation with our study design is the strict inclusion and exclusion criteria potentially causing problems in generalising the results to larger groups of depressed pregnant women. So far, we have not seen any tendencies to exclusion of relevant subgroups. The most common reason for exclusion so far has been not having a severe enough, treatment requiring depression. We collect baseline data from all excluded patients to stay informed about potential statistical biases caused by exclusion. We also know, that the recruitment will be challenging, considering the limited study population of clinically depressed, pregnant women without medical treatment with a short time frame for recruitment. We have addressed this using a combined approach recruiting both at ordinary antenatal clinics and through social media, pregnancy applications on smart-phones as well as with marketing campaigns. Studies worldwide show that three out of four pregnant women use a pregnancy related application, showing their great potential.[45,46] Our web-based recruitment and treatment also gives us the possibility to invite additional study centres across the country if necessary to complete the recruitment. We are constantly facing fears from potential subjects of taking antidepressant

treatment during pregnancy.

We have been working with this study for four years, specifying and completing the protocol and getting ethical approval and permission from the national Medical Products Agency. In addition, it has taken an additional year to test the feasibility by completing the first five patients through the pregnancy and delivery parts of the trial (January 2018). During these five years, the multidisciplinary research group with less and more experienced members has had regular meetings. So far, we have not met any problems in raising needed funds, received both from major national and regional funders of clinical research as well as from multiple funders specialized to support studies on safe care of mother and child during pregnancy and in early life. Therefore, we are confident to finish the recruitment within six years, based on our calculations on data from Stockholm Healthcare Region (Figure 2) and publish the results in another three years.

Declarations

Ethics approval and consent to participate

The Regional Ethical Review Board at Karolinska Institutet in Stockholm approved this study with the approval number 2014/952-31 with the last amendment approved 20170116. The Swedish Medical Products agency approved this study with the approval number 5.1-2016-51237 with the last amendment approved 20160701. Written consent is obtained from all participants at inclusion. At child birth, written consent is obtained from the child's other guardian. All protocol amendments are sent to the Regional Ethical Review Board and the Medical Products Agency for approval before taken in practice. A copy is also sent to the registrator at clinicaltrials.gov.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EH and LLG wrote the initial study protocol article with the help of BSS, LF and AF. KW is the principal investigator and JN, LLG, MB and VK are members of the governing study

board. MB is the sponsor and the main applicant and receiver of our initial ground-breaking funding decision from the Swedish Research Council. MB is also a senior researcher with full responsibility of the study design and participation in completion of the manuscript.
JN, KW and MB conceived the study protocol and KW wrote the initial draft of the study protocol. EA is developing an exploratory study protocol studying attachment in a subgroup of the pregnant women. MBk, SF and EH launched the open recruitment through different social media platforms. VK and EF adapted the ICBT procedure for use in our pregnant women and are responsible for the ICBT treatment. They also directed the pilot study. AF is the study midwife coordinating the visits and the day to day management of the study. M.B-W, MS and AJ are the study psychiatrists responsible for the initial assessment and inclusion in the study as well as for the clinical decisions about pharmacotherapy. E-M.N is the psychiatry nurse responsible for the treatment evaluations. All authors have in different ways been involved in different degrees in the development of study design and take responsibility for the final study design. All authors have contributed to the protocol development and have read and approved the final protocol that we now use after revisions as well as this manuscript. EH and LLG coordinated the completion of the study protocol article.

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Trial Registration and Status

European Clinical Trials Database (EudraCT) Number: 2013-004444-31. Date registered 20140511. Current protocol version 5.2 161121. Recruitment start 2016. Approximate completion of recruitment 2023, approximate completion of data collection 2025.

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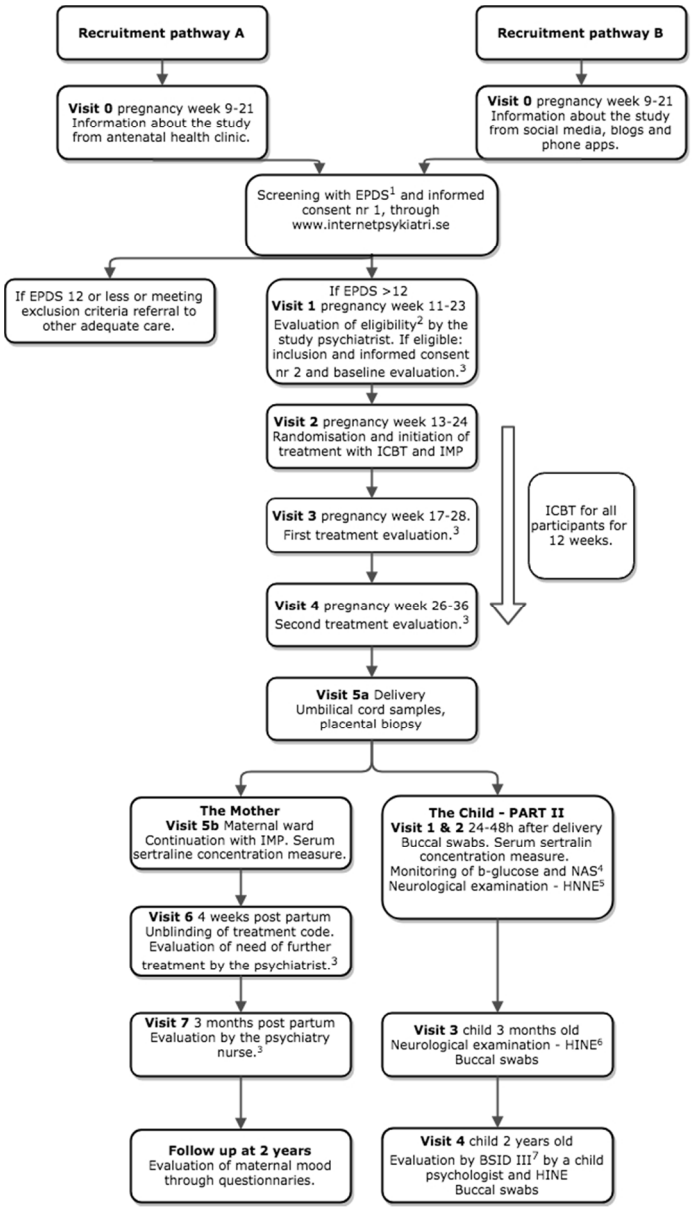

Figure 1. Trial design and participant timeline for the two recruitment pathways. The figure also shows the treatment with placebo/sertraline from visit 2 (pregnancy week 13-24) to visit 6 (4 weeks postpartum) and the ICBT for both groups for 12 weeks, between visit 2 and visit 4 (pregnancy week 26-36) and monitoring of therapy for the two groups. The post-partum follow-up of both mother and child are shown. The different scales and examinations are, as presented in the figure: 1) Edinburgh Postnatal Depression Scale (EPDS)39, 2) The diagnose moderate depression is confirmed according to clinical standard evaluation. Inclusion and exclusion criteria presented in table 1. 3) Evaluation with Montgomery-Åsberg Depression Scale (MADRS)40, 4) Modified Finnegan Neonatal Abstinence Scale (NAS)41, 5) Hammersmith Neonatal Neurological Examination (HNNE)42, 6) Hammersmith Infant Neurological Examination (HINE)43, 7) Bayley Scales of Infant and Toddler Development III (BSID III)44.

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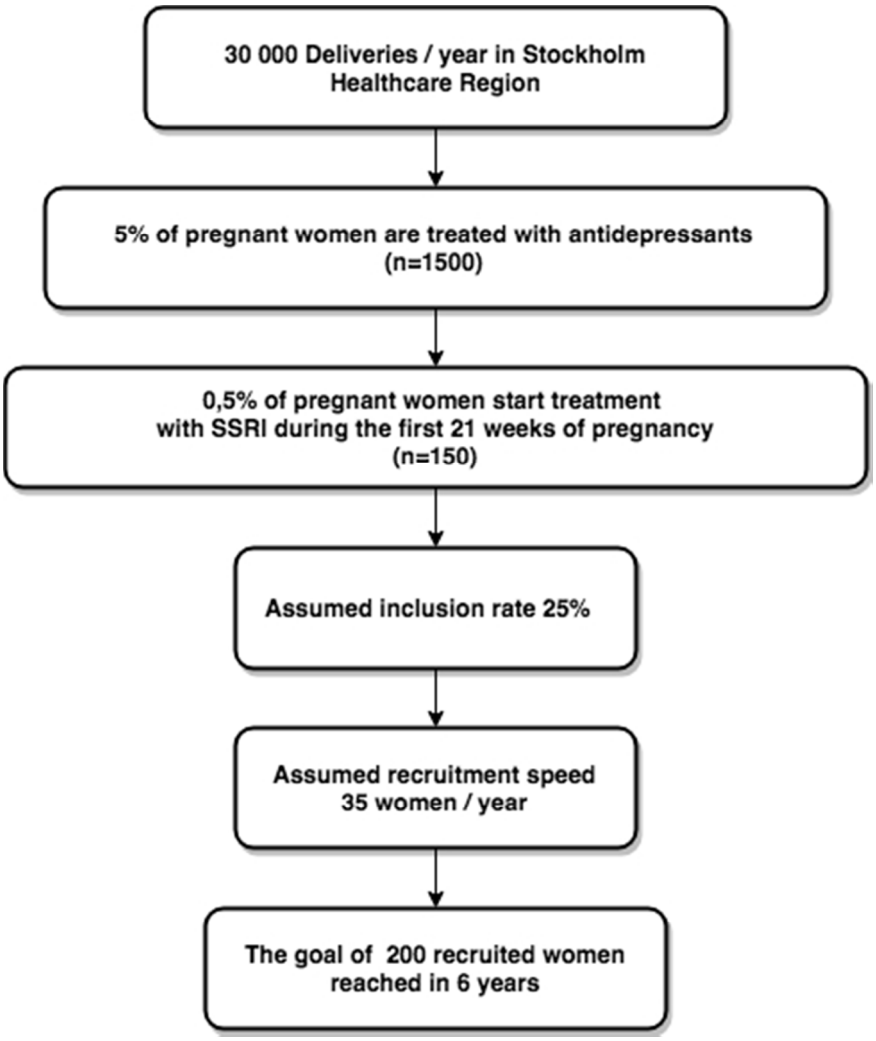

Figure 2. The recruitment base in Stockholm Healthcare Region. Numbers based on an analysis of prescription of SSRI:s in pregnant women in years 2013-2016 in the Stockholm healthcare region with 2,3 million inhabitants Acknowledgements).

153x181mm (72 x 72 DPI)

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 13
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions:	#11a	Interventions for each group with sufficient detail to	7

description		allow replication, including how and when they will be administered	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 (fig1)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any	6

		planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5,6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the	9

		protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial	13

		registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5, fig1
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Use of professional writers not intended
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Publication of full protocol possibly with this manuscript.

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Are attached. English translations can be published as appendices.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

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MAGDALENA: Study protocol of a randomised, placebo-controlled trial on cognitive development at two years of age in children exposed to SSRI in utero.

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MAGDALENA: Study protocol of a randomised, placebo-controlled trial on cognitive development at two years of age in children exposed to SSRI in utero.

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ABSTRACT

Introduction

Ten percent of all pregnant women are depressed. Standard therapy of pregnant women with moderate depression is Selective Serotonin Reuptake Inhibitors (SSRI). Observational studies on neurodevelopment after fetal SSRI exposure show conflicting results. Our primary objective is to compare the cognitive development in children exposed to sertraline and maternal depression with those exposed to maternal depression and placebo *in utero*. We

hypothesize that there is a significant neurodevelopmental differences between the groups. As a secondary objective we study the add-on effect of sertraline to Internet-based Cognitive Behaviour Therapy (ICBT) to treat moderate depression during pregnancy.

Methods and analysis

MAGDALENA is a randomised, placebo-controlled, double-blinded trial in Stockholm Healthcare region with 2.3 million inhabitants. The women are recruited in week 9-21 of pregnancy either through Antenatal Health Clinics or through social media. They are to be diagnosed with moderate depression without ongoing antidepressive therapy or any serious comorbidity. The women in the intervention arm receive sertraline combined with a twelve-week period of ICBT, the control arm is treated with placebo and ICBT. We assess the cognitive development in the offspring at the age of 2 using Bayley Scales of Infant and Toddler Development®, 3rd edition (BSID-III®). We aim at recruiting 200 women, 100 women in each treatment arm, to ensure statistical power to detect a clinically relevant difference between the groups.

Ethics and dissemination

This randomised trial will provide long sought evidence about the effects of SSRI and maternal depression during pregnancy on the neurodevelopment in the offspring. The study is approved by the Regional Ethical Review Board at Karolinska Institutet in Stockholm and the Swedish Medical Products Agency. It is registered with the European Clinical Trials Database (EudraCT), Number: 2013-004444-31. Results will be disseminated at scientific conferences, published in peer-reviewed journals, and made available to the public.

Key Words: Antenatal depression, Drug metabolism, Infant, Internet-based Cognitive behaviour therapy, Neurodevelopment, Pregnancy, Randomised controlled trial, Serotonin Reuptake Inhibitors,

Article Summary

Strengths and limitations of this study

+ To our knowledge, this is the first randomised controlled trial to separate the neurodevelopmental effects of fetal SSRI exposure from the possible effects from the underlying maternal depression. We consider that a randomised controlled trial is the most valid method to find answers to this complex question.

+ The highly structured and homogenous nature of the ICBT given to both groups reduces the risk of confounding by therapist factors and should make the add-on effects of sertraline clear-cut.

- The ICBT protocol is in Swedish only and cannot be performed with an interpreter which requires Swedish literacy. Therefore the generalizability of our study results is reduced and the recruitment potential limited in multicultural areas.

- The severity of depression is monitored with MADRS, which contains items that can be related both to depression and to pregnancy which complicates the interpretation of the results.

- Due to the evaluation at 2 years of age, we cannot answer the question about autism, since it is not easily diagnosed at this early age. We plan to follow up our cohort long-term.

Word Count: 5670 words (Excluding title page, abstract, figures, tables, declarations and references.) Abstract 298 words.

Introduction

Background

Although approximately ten percent of pregnant women are depressed, the prescription-rate of antidepressants decreases during pregnancy as compared to the preceding months [1-3] Untreated prenatal depression is associated with pregnancy complications such as preeclampsia[4], low birth weight and prematurity[5] and increased plasma levels of stress hormones in the pregnant woman and the neonate.[6,7] Published data shows, that 2,4% of pregnant women in Sweden during years 2006-2012[8] and 6% of the ones in USA during the years 2001-2013[9] were treated with SSRIs. Our own unpublished data of prescriptions for Stockholm Healthcare Region extracted from the Swedish Drug Registry shows, that this percentage is constant at 5% in pregnant women in Stockholm during the period 2014 to 2016. Increased risk for SSRI-related birth-defects has not been reported for most SSRIs except that fluoxetine and paroxetine seem to be associated with a small increase in the risk for heart defects.[10]

The question if fetal SSRI exposure causes long-term neurodevelopmental effects remains unanswered.[11] Observational studies have reported a twofold increased risk for autism spectrum disorder (ASD),[12-15] but recently two large register studies explained this increase by confounding factors, emphasizing the role of genetic and social factors as opposed to drug exposure alone.[16,17] A recent review also concluded, that the increase was not significant when comparing to women with previous affective disease or in sibling studies.[18] To our knowledge, there is no previous randomised controlled trial in this field.

Our main objective is to clarify the cognitive effects on the children by pursuing a randomised, controlled, double blind study. We compare the cognitive development at two years of age in children to women with moderate depression during pregnancy, treated with either Internet-based Cognitive Behaviour therapy (ICBT) and sertraline (a SSRI compound) or ICBT and placebo. The Swedish acronym of the study, MAGDALENA, reflects this main objective: *"Maternal Affective Disease during Pregnancy: Depression and Antidepressant*

Drugs and Effects on the Neurological Development and Adaptation".

Our secondary objective is to understand the add-on effect of sertraline to Internet-based Cognitive Behaviour Therapy (ICBT), a web-based self-treatment program with active therapist support over the internet. ICBT is a well-documented treatment for depression used in regular psychiatric care.[19] It has been shown that pregnant women feel that psychotherapy needs to take the special case of being pregnant into account to be credible and engaging.[20] Postpartum depression has been targeted in online trials,[20-23] but not antenatal depression. Because of this, we developed an ICBT program to be useful for treatment of antenatal depression based on the ICBT for depression used at our Internet Psychiatry Clinic. The modified ICBT was tested in a pilot RCT with good results. The effect size compared to regular maternity care was of clinical importance and significant, (Hedges g=1.21, p<.001)[24] The Swedish guidelines state that mild and moderate depression should primarily be treated with psychotherapy or antidepressants. Cognitive behaviour therapy and interpersonal therapy are recommended as the first choice of therapy. Severe depression should be treated with antidepressants or electroconvulsive therapy (ECT). The recommendation does not give guidance on the value of combination therapies for any level of depression.[25] Combination therapy with CBT and antidepressants appear more effective than antidepressant therapy alone in treatment of major depression,[26] but this has not been studied in pregnant women. Given the *in-utero* effects of untreated depression during pregnancy,[7] it might be rational with a dual treatment to achieve prompt symptom reduction. The effects of ICBT are comparable to the effects seen with traditional CBT, hence having the potential to be a cost-effective and accessible treatment alternative.[19,24,27,28] Our large group of patients and unique design with and without sertraline treatment allows us also to pursue exploratory tertiary studies in the pregnant women and in the newborns.[29,30]

Objectives

Primary and secondary objectives

Our primary objective is to study cognitive development at 2 years of age in children prenatally exposed to moderate maternal depression treated either with sertraline and ICBT (Intervention) or with ICBT and placebo (Control). Our hypothesis is that there is a significant neurodevelopmental difference between 2 year old children exposed to the intervention treatment (sertraline) as compared to the control treatment, measured with established scoring methods. If no difference is detected we will include a non-inferiority analysis to test if the neurodevelopment in the exposed group is at least as good as for the control group of children.

Our secondary objective is to evaluate the add-on effect of treatment with sertraline to an ICBT-program for antenatal depression. Our hypothesis is that sertraline provides a significant add-on effect to ICBT-therapy.

Exploratory tertiary objectives

The large material and unique design with one SSRI-exposed and one placebo-treated arm allows exploratory studies on tertiary aspects related to physiological and adaptive changes in

depressed pregnant women and in their newborns. We will study the risk of preeclampsia, bleeding and caesarean section and potential changes of biochemical parameters and hormones during the course of pregnancy in the two study groups.[4 31-33] Paediatric exploratory objectives include clarification of type and prevalence of signs and symptoms of neonatal maladaptation and risk of admission to a neonatal care unit. The design allows a subgroup study of maternal-fetal attachment and bonding style differences between the groups.[34]

We will explore interindividual variation in sertraline pharmacokinetics during and after pregnancy and in newborns and how it might relate to different genetic variants of drug metabolizing enzymes in pregnant women and newborns.[35-37] Likewise we will explore the epigenetic differences between the groups in mothers and newborns.[38]

Methods and analysis

Trial design and setting

The MAGDALENA Study is a prospective, randomised, placebo controlled, double blinded, single centred, clinical investigation of pregnant women with moderate depression recruited from the Stockholm catchment area (2.3 million inhabitants and 28000 deliveries annually) with multiple delivery units. The study group receives sertraline (or placebo) clinically titrated to a maximum daily dose of 150 mg. The study and control groups are both treated with ICBT.[24] The trial design includes two different recruitment pathways (A and B) (Figure 1). The primary outcome is achieved with scoring of the neurodevelopment of the child at 2 years of age. The framework for neurodevelopment is primarily a superiority test. The add-on effect of SSRI to ICBT is also a superiority test. The tertiary objectives are exploratory.

Figure 1. Trial design and participant timeline for the two recruitment pathways. The figure also shows the treatment with placebo/sertraline from visit 2 (pregnancy week 13-24) to visit 6 (4 weeks postpartum) and the ICBT for both groups for 12 weeks, between visit 2 and visit 4 (pregnancy week 26-36) and monitoring of therapy for the two groups. The post-partum follow-up of both mother and child are shown. The different scales and examinations are, as presented in the figure: 1) Edinburgh Postnatal Depression Scale (EPDS)[39], 2) Diagnosis of moderate depression is confirmed according to clinical standard evaluation. Inclusion and exclusion criteria presented in table 1. 3) Evaluation with Montgomery-Åsberg Depression Scale (MADRS)[40], 4) Modified Finnegan Neonatal Abstinence Scale (NAS)[41], 5) Hammersmith Neonatal Neurological Examination (HNNE)[42], 6) Hammersmith Infant Neurological Examination (HINE)[43], 7) Bayley Scales of Infant and Toddler Development III® (BSID III®)[44].

Recruitment and blinding

Pregnant women are recruited either from the antenatal health clinics (Figure 1, Pathway A) or through social media and our study website www.magdalenastudien.se (Figure 1, Pathway B). Pregnant women visit their midwives at the antenatal clinics, commonly with their partners, around ten times during pregnancy free of charge. In pathway A, the midwives

inform about the study at a regular visit. The recruitment through the study website, pathway B, is simplified by informing about the study to potential subjects continuously through social media, pregnancy related information platforms, different blogs and podcasts. Smartphone pregnancy applications are popular, reaching about 75% of pregnant women in cross-sectional studies in English and Spanish speaking countries. We assume similar, if not higher, usage in Sweden.[45,46] In both pathways, the women are directed our study platform at the internet psychiatry website, www.internetpsykiatri.se. They are asked to fill the Edinburgh Postnatal Depression Scale (EPDS)[39] self-test to assess the degree of depressive symptoms as well as to sign the first informed consent form. Regardless of recruitment pathway, the women will continue their regular visits at their home antenatal clinic.

We have chosen 13 or more points on the EPDS for further evaluation of eligibility for the study. The reason is that it has been found to be the optimal cut-off point with 77% sensitivity and 94% specificity for detection of depressive symptoms during pregnancy.[39] The subjects scoring 13 points or more on the EPDS self-test and lacking exclusion criteria are scheduled to meet one of our three study psychiatrists for clinical evaluation, including SCID-I directed interview (Structured Clinical Interview for DSM IV axis I disorders)[47], review of eligibility criteria and signing of the final informed consent form. (Visit 1, Fig.1, Table 1). The included women are allocated to the next consecutive patient number and randomised to treatment by Karolinska Trial Alliance (KTA), see below. The KTA will also ensure correct blinding for all trial participants, care providers, outcome assessors and data analysists, including labelling of the study drug packages. The drug treatment with study drug (sertraline or placebo) is initiated after visit 2 (Fig.1). At the same time, the women start ICBT treatment using the internet psychiatry website.[19,24] Both study and control groups receive capsules of identical appearance and packing (See below). The treatment code is broken and a new clinical evaluation is performed by the study psychiatrist one month after the delivery. The treatment will be continued for one year after the delivery for all patients in the active treatment arm. The women in the placebo group that haven't reached remission will also be offered treatment with SSRI. Both the women and the psychiatrist are forbidden to inform anyone in the study about which group they have belonged to, to ensure the continued blinding of the study. This is particularly important regarding the paediatricians and paediatric psychologists assessing the children.

Inclusion Criteria	▪ Age >18 years ▪ Pregnant in week 9 to 21 after last menstrual period. ▪ Verified moderate depression according to SCID-I (with or without a concomitant anxiety disorder) and a clinical evaluation. ▪ Ability to use the internet platform for ICBT in Swedish as assessed by the study midwife. ▪ Reported ability to participate in all study visits for mother and child.
Exclusion Criteria	▪ Reported abuse of alcohol or drugs ▪ Reported serious psychiatric disorder[1] ▪ Known allergy or idiosyncratic reaction to sertraline ▪ Ongoing medication with antidepressants, mood-stabilizers, central stimulants, antiepileptic drugs, opiates, insulin, oral anti-diabetics, antiarrhythmics or steroids. ▪ A severe somatic disease[2] that requires medical treatment. ▪ A high suicidal risk during screening or when included into the study. These women will be excluded from the study and actively transferred to necessary psychiatric care.

Table 1. Inclusion and exclusion criteria for the MAGDALENA study. [1)] Psychosis, bipolar disorder, severe melancholic or psychotic depression, severe personality disorder, autism, mental retardation or Attention Deficit and Hyperactivity Disorder (ADHD)/Attention Deficit Disorder (ADD) with ongoing drug treatment or contact with specialist psychiatry clinic[2)] Severe heart and lung disease, kidney disease, liver disease, diabetes mellitus, epilepsy with drug treatment and any severe somatic disease that requires regular treatment with systemic steroids.

Figure 2. The recruitment base in Stockholm Healthcare Region. Numbers based on an analysis of prescription of SSRIs in pregnant women in years 2013-2016 in the Stockholm healthcare region with 2.3 million inhabitants. See Acknowledgements.

The study drugs

Sertraline is one of the two first-line recommended drugs for depression during pregnancy according to the Drug and Therapeutics Committee in Stockholm Healthcare Region.[48-50] Sertraline is also widely used across Europe for treatment of depression during pregnancy.[3,51,52] This is why sertraline was the preferred choice as the study drug.

The investigational medicinal product (IMP) is a capsule containing either sertraline hydrochloride or placebo manufactured by APL (Apoteket Produktion & Laboratorier AB, Stockholm, Sweden). The capsules of active drug are made of hard gelatine and filled with sertraline hydrochloride corresponding to 25mg sertraline using Zoloft® (25mg sertraline film-coated tablets, Pfizer Ltd, New York) and with a microcrystalline cellulose filler. The placebo capsules are made of identical microcrystalline cellulose filler embedded into an identical hard gelatine capsule. The IMP is delivered by the producer in sealed HD polyethylene containers, labelled according to a randomisation list. Patients are randomised to treatment by Karolinska Trial Alliance (KTA) with block randomisation. The size of these blocks is blinded for the investigators.

The treatment with sertraline (or placebo) starts with titration of a dose of 1 capsule (25 mg sertraline or placebo) once daily for 5 days, after which the dose is increased to 2 capsules (50 mg of sertraline or placebo) once daily until the first treatment evaluation (Visit 3, Fig.1). At

visit 3 the daily dose can be increased to 4 capsules (100 mg of sertraline or placebo) once daily if clinically indicated, with titration of 3 capsules (75 mg of sertraline or placebo) once daily for 5 days. At visit 4 after 13 weeks of treatment, the dose can be increased further to a maximum 150 mg daily, without titration, if clinically needed. The decision of need to increase drug dosages is based on MADRS scores and a clinical evaluation made by the study psychiatrist. To follow and increase the adherence to treatment, the women will get a limited amount of capsules at each visit, motivating them to return for the next visit and giving the study midwife a way to notice if the subject is not taking the drug. Additional telephone contacts with the psychiatry nurse are performed if concerns about the treatment effect are raised, and an additional visit to the psychiatrist is scheduled if necessary. The study protocol attached as an appendix gives a detailed description of the treatments, monitoring of mothers and follow-up of both mothers and infants.

The Internet-based Cognitive Behaviour Therapy

The ICBT-treatment is 12 weeks long and guided by a psychologist who is available online. It consists of an online platform where patients log in to answer questionnaires and work with self-help material covering the core materials in CBT for depression including interactive worksheets and exercises. They are also assigned weekly homework to report to their personal therapist. A direct messaging system allows for asynchronous correspondence with one of the therapists at any time and get a reply within a day or two. The platform allows monitoring to what extent the patients adhere to the therapeutic sessions.

The pregnancy-related adaptations of the ICBT-treatment consist of an extra module on pregnancy related symptoms that can lower mood at the beginning of the treatment and an extra module on relationships at the end of treatment. Other than that, the interventions mostly mirror those described and used by us in our ICBT-platform for non-pregnant adults.[19] The examples and cases includes concern pregnant women and their thoughts on pregnancy and becoming a parent and expanding their family. The core methods of the treatment are behavioural activation (increasing positive and valued activities) and cognitive restructuring (challenging own thoughts and distance oneself from dysfunctional thoughts and rumination).

Outcome measurements

Primary outcome: effect on neurodevelopment at 2 years of age

The cognitive development at 2 years of age is the primary outcome. The outcome in children exposed and not exposed to sertraline *in utero* is measured with the standardized Bayley Scales of Infant and Toddler Development III (BSID-III®)[44] and compared between the groups. The BSID-III consists of the Cognitive, Language and Motor Scales that are performed by a child psychologist, and the Social Emotional and the Adaptive Scales that are parental questionnaires. The Cognitive and Language scales have proven to be good predictors of preschool mental test performance.[53] These scales are largely used in screening for cognitive developmental delays,[54] and have been used in studies of cognitive development after intrauterine drug exposure.[55-57] Results from the subscales will be converted to composite scores with a median of 100 and a standard deviation of 15. For each subscale, a composite score of <85 (<-1SD) will be considered abnormal. A difference of 7 points (0.5

SD) between the groups will be considered significant, which is in line with the assumptions made in previous similar studies.[54]

Sample size calculation

A difference of 7 points (SD 0.5) in the results of BSID-III at 2 years of age is considered a minimally important clinical difference, based on the previous follow-up studies performed with BSID.[56,58,59] We calculated, that with a power of 80% (α: 0.05), this would show a significant difference in a sample of 73 participating children in each group. We hypothesise that there is a significant difference between the groups and have performed a calculation for a superiority test (effect on BSID for the sertraline exposed study group). We aim at recruiting 100 mothers in each group to rely on a result that has a margin for loss to follow-up, considering the long-term nature of this study. If no difference is found our study design will also provide enough power to test the non-inferiority hypothesis. According to a non-inferiority power calculation method[60] we will need 50 patients in each group to have power of 80% (α: 0.05) to confirm that the SSRI-exposed children lies within a tolerance margin of 7 points below the control children. This corresponds to an effect size of 0.5 (Cohen's d). As a more conservative sensitivity test for non-inferiority, we will also use a tolerance margin of 5 points, which would correspond to an effect of d=0.36. This requires 97 patients in each group.

Secondary outcome

The main psychiatric secondary outcome is the add-on effect of sertraline to the treatment with ICBT on depressive symptoms measured with MADRS-S (Montgomery-Åsberg Depression Rating Scale, Self-Report)[61] which is performed weekly throughout the 12 week treatment period.

Sample size calculation for the secondary outcome

The additional effect of sertraline as compared to standard ICBT plus placebo will be evaluated by comparing effects on MADRS-S scores between the groups. Data on the total effect of CBT combined with antidepressant therapy is limited. The standardized effect of psychotherapy can be as high as 0.74 when compared to placebo and 0.38 when compared to face-to-face psychotherapy.[26] ICBT is largely self-directed even with therapist guidance, which is likely to put a higher demand on the patients in terms of initiative and maintaining the motivation compared to face-to-face-treatment. Therefore, it is likely that the added effect of SSRI will be larger than what has been found in face-to-face CBT, though not as large as when compared to placebo alone. We therefore hypothesize a standardized effect size of *d*=0.50 (Cohen). This is also the minimal added effect that we would consider clinically relevant considering the possibility of negative side effects and the documented efficacy of ICBT alone.[24] A sample size calculation with standardized effect equal to 0.5 (Cohen), alfa-value=0.05 and power 80% requires 64 persons in each group. Therefore to recruit 100 patients in each group will fulfil the power calculation.

Exploratory tertiary studies

Exploratory maternal outcomes include the effects on levels on prolactine and cytokines and the risk for postpartum bleeding measured in mL and postpartum anaemia measured with haemoglobin day 2 for the SSRI-exposed women as compared to the placebo-exposed. We also evaluate the risk of preeclampsia, placental abruption and increased caesarean section rate.

The neonatal exploratory outcomes include admission to neonatal care, neurological evaluation with Hammersmith Neonatal Neurological Examination (HNNE)[42] and modified Finnegan Neonatal Abstinence Scales (NAS)[41] and measurement of glucose and concentrations of sertraline in plasma.

In a sub-cohort, blood samples from the umbilical cord and placental biopsies are taken to study epigenetic effects (DNA methylation, genome width, and gene and mRNA expression) between SSRI-exposed and the non-exposed within this cohort.

We will study differences in maternal-child bonding/attachment during and after birth and also breastfeeding occurrence. Prenatal Attachment Inventory-Revised questionnaires and video recordings analysed by "Dr Feldman's micro-coded behaviours" will be used which is a valid tool to study attachment.[62] A comparison will be made between the two groups.

The pharmacokinetic analyses include studies of interindividual variability in plasma sertraline concentrations and its change during the course of pregnancy and postpartum (mean concentration/ (dose in mg/kg) with confidence intervals. Pharmacogenetic variants of drug metabolizing enzymes and transporters will be studied in pregnant women and newborns. Umbilical cord blood and venous blood from the neonate will be taken and plasma sertraline levels are assayed. Variability in exposure to sertraline between the neonates will be investigated and the levels will be related to the degree of maladaptation syndrome.

Data management

Each subject will receive a study number for identification. Data will be collected continuously and entered into the electronic Case Report File (eCRF) within two weeks from collection. The e-CRF includes range checks for data values to promote data quality. For the study database we are using an electronic system, Pheedit version 3,0; SAS Institute Inc., Cary, NC, provided by Stockholm Healthcare Region, Sweden. The data is encrypted and safely stored on an electronic server at the Karolinska Institute in Stockholm. The e-CRF is previously used in randomised controlled studies.[63] After completed data collection, the investigators will receive unidentified patient data withdrawn from the CRF and synchronized with data from the internet psychiatry platform. The internet psychiatry platform was also used in our previous study.[24] The investigators will analyse this data for the different endpoints of the study. The samples from whole blood (mainly to extract DNA for pharmacogenetic analyses in the mother and in the newborns), plasma, cord blood, placenta biopsies and the buccal swabs will be stored in the biobank at Karolinska Institutet in Stockholm, available for analyses and future research.

Statistical Methods

The main analyses will be done according to the intention to treat principle. Data will also be analysed per protocol to achieve an efficacy analysis. The primary endpoint, results of BSID III® will be analysed with Student's T-test. According to the hypothesis for the primary objective a superiority analysis will be carried out. In case of no difference in BSID-scores non-inferiority analyses with a tolerance level of 7 points in the BSID III® will be used. We may also include a more conservative sensitivity analysis using a tolerance level of 5 points.

Multiple imputation will be used for missing data. The variables used in the imputation mode will be smoking, education level, gestational age and parity. Preterm children will be included in the analysis as the chosen psychological and neurological tests are performed at corrected age. All patients' demographic data will be analysed by descriptive (mean, median and range) statistics. Fisher's exact test will be used for dichotomous variables such as infant sex, mother's smoking and optimal/suboptimal neurology at Hammersmith neonatal neurological examination. Throughout the analysis, the mean and standard deviation will be calculated for all continuous data using Student's T-test. The non-normally distributed continuous variables, including the results from Hammersmith neurological scales will be analysed with the Mann-Whitney u test and the results of MADRS-S by Cohen's effect size. For categorical variables, absolute frequency, percentages and/or proportions are calculated and Fishers exact test will be used. The treatment effect analysis will be a multilevel model for longitudinal data with timepoints nested within individuals (a.k.a. Growth Curve Modeling) using MADRS-S scores from baseline, each of the 12 weeks in treatment, and post treatment. A p-value of <0.05 will be considered significant. Subgroup analyses will be performed for prematurity, smokers, parity, maternal age and education level. Spearman's correlation test will be used to test the correlation between maternal and infant drug concentration.

Patient and Public Involvement

No patients or public have been involved in the design, recruitment or conduction of the study.

Ethics and dissemination

Ethics approval and consent to participate

The Regional Ethical Review Board at Karolinska Institutet in Stockholm approved this study with the approval number 2014/952-31 with the last amendment approved 20180507. The Swedish Medical Products Agency (SMPA) approved this study with the approval number 5.1-2016-51237 with the last amendment approved 20160701. The included Appendix to this article includes a few clarifications in the protocol and is submitted to the Regional Ethical Review Board and the SMPA to be approved as an amendment. Written consent is obtained from all participants at inclusion. At the end of the pregnancy, written consent is obtained from the child's other guardian. All protocol amendments are sent to the Regional Ethical Review Board and the Medical Products Agency for approval before taken in practice. A copy is also sent to clinicaltrials.gov.

Adverse events

Sertraline is one of the recommended drugs for depression during pregnancy in Stockholm Healthcare Region by the Drug and Therapeutics Committee with high adherence.[49,50] Sertraline is also one of the most prescribed SSRIs in the Nordic countries, and is widely used

across Europe for treatment of depression during pregnancy.[3,51,52] Thereby the therapeutic profile, the adverse effects and the adverse reactions are well known to the study psychiatrists.

An adverse event (AE) is defined as any undesirable experience associated with the use of the trial drug, sertraline or placebo. A serious adverse event (SAE) is defined as death, a life-threatening event, hospitalization (initial or prolonged), disability, permanent damage or a congenital birth defect. Expected serious adverse reactions are listed in the Summary of Product Characteristics (SPC). A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an adverse effect not listed in the SpC and not mentioned in the SPC as anticipated due to pharmacokinetic properties of the drug, or as a reaction that has occurred with other drugs in this class, but not with the study drug. Unexpected adverse events to ICBT will also be reported. All adverse events occurring after enrolment are documented in the electronic Case Report Form (e-CRF). The adverse events will be reported to the principal investigator, who will report to the sponsor, and in due cases the Karolinska Trial Alliance (KTA) for registration in EduraVigilance. All unexpected serious adverse reactions have to be reported within 24 hours after notification by the study personnel. In case of a serious adverse event such as death or a life threatening event, the PI will raise the issue of breaking the code and termination of the study with the Data Monitoring and Safety Committee (see below). The committee are responsible for the final decision of study termination. The sponsor will each year of the study perform a safety report (DSUR) to Swedish Medical Products Agency.

Monitoring and Study safety

An independent monitor from Karolinska Trial Alliance (KTA), Karolinska University Hospital, will continuously control that the study follows approved protocol, with regular audits with the study midwife and the PI. The staff at KTA have all relevant certifications for Good Clinical Practice (GCP) procedures. Participation in the study is voluntary and women are free to discontinue their participation at any time and for whatever reason without explanations. Midwives at the outpatient clinics and at the delivery clinic have been made aware of this. A Data Monitoring and Safety Committee (DMC) with senior experts in biostatistics, psychiatry, clinical pharmacology (sub-specialised in paediatrics) and neonatology. The committee can at any time if there is any suspicion of a serious adverse event break the code and undertake necessary precautions including stopping the study. The committee is independent from the sponsor with no competing interests or involvement in the design, planning or management of the study. The DMC is also responsible for developing guidelines for interruption of the study and for any interim analyses. The DMC is responsible for deciding if sub-study exploratory investigations can be carried out before the recruitment of all 200 mothers and all 2-year neurodevelopment investigations are completed.

Dissemination plan

This study has as main aim to clarify if any long-term effect on neurodevelopment can be detected in children exposed to sertraline therapy *in utero*. Other issues will be studied as secondary and tertiary objectives including evaluation of the add-on effect of sertraline to ICBT in moderately depressed pregnant women. The study team will design and implement a

knowledge translation (KT) plan using established methods for dissemination of scientific results but also modern communication strategies using social media. The KT plan will benefit from strength of being a multidisciplinary scientific group with access to numerous regional, national and international scientific and clinical communities and active involvement of many of the study group scientists in communication with patient groups on psychiatric health and drug therapy during pregnancy. The team has combined years of experience to communicate with colleagues on drug recommendations and achieve high adherence to them using a combination of multifaceted (marketing, continuous medical education, decision support and quality network with colleagues).[49,50] In summary we will use established scientific channels to communicate our findings (A): 1. At national and international scientific meetings, 2. As international scientific publications including publishing our study protocol and 3. By contacting relevant international bodies for development of guidelines on best practice in treatment of psychiatric diseases during pregnancy including WHO. We will also use modern communication methods[49,50] (B): 1. To summarize our findings for laymen and pregnant groups in Swedish and English and 2. To cooperate with these groups to have information disseminated through their publications and websites. Our aim is to improve knowledge about the need to a higher degree treat depression during pregnancy with the alternatives that we and others have found effective. If we, as hypothesized, will find no effect of sertraline therapy on neurodevelopment in two year old infants, it will be one of the most relevant findings to communicate scientifically and to laymen. The legitimacy of our findings will be high if the results are published in peer-reviewed journals and presented at national and international scientific conferences for scrutiny and discussion.

Discussion

We hypothesise that sertraline exposure in therapeutic dosage during pregnancy can cause a recognizable effect on the cognition in the offspring as assessed by BSID-III® at 2 years of age. A balanced review supports this hypothesis.[11] Recent large register based studies[16,17] imply the importance of a randomised controlled trial to receive sound evidence in this question. As the previous observational studies comment,[12,13] they have not found a way to adequately adjust for unmeasurable confounders, such as genetic inheritance and disease severity, that we suspect play a significant role when interpreting the results. Using a randomised design in the MAGDALENA study, we minimize the risk for confounding factors.

We also aim to clarify whether combination therapy with ICBT and sertraline is an adequate treatment alternative for moderate depression during pregnancy. This new treatment option provides the pregnant women relevant pregnancy-related questions and the possibility to individually schedule the treatment sessions. Also to our knowledge, no prior placebo-controlled clinical trials have assessed whether combination treatment is superior to treatment with ICBT alone, which we are doing. The risks for the participating women and their offspring are not increased compared to the regular treatment available, as sertraline is widely used in clinical routine in Sweden today. On the contrary, the participating women will have a more thorough follow up than in clinical practice.

The ethics of performing a RCT in this field has been discussed.[64,65] Our study design with ICBT and sertralin or placebo for depression during pregnancy was enabled by recent studies that confirmed the safety and efficacy of ICBT in treating depression, including prenatal

depression.[24,28] To date, there is to our knowledge no other study group performing a similar study with the neurodevelopment of the offspring as the main outcome measure. An ongoing Dutch study group randomise clinically undepressed women on antidepressive treatment to either guided drug discontinuation with CBT or continuation of drug therapy.[66] Their primary outcome is the incidence of relapse or recurrence of maternal depression, but they also look at the long-term neurodevelopment with questionnaire based follow-up at 18 months. We consider our method with psychological assessment at 2 years of age more reliable than parental questionnaires. We think that these two studies will complement each other well. Our study will have the unique opportunity to distinguish the effects of exposure to SSRI in utero from the ones of underlying depression, considering our inclusion criteria of moderately depressed women.

A limitation with our study design is the strict inclusion and exclusion criteria potentially causing problems in generalising the results to larger groups of depressed pregnant women. So far, we have not seen any tendencies to exclusion of relevant subgroups. The most common reason for exclusion so far has been not having a severe enough, treatment requiring depression. We collect baseline data from all excluded patients to stay informed about potential statistical biases caused by exclusion. We also know, that the recruitment will be challenging, considering the limited study population of clinically depressed, pregnant women without medical treatment with a short time frame for recruitment. We have addressed this using a combined approach recruiting both at ordinary antenatal clinics and through social media, pregnancy applications on smart-phones as well as with marketing campaigns. Studies worldwide show that three out of four pregnant women use a pregnancy related application, showing their great potential.[45,46] Our web-based recruitment and treatment also gives us the possibility to invite additional study centres across the country if necessary to complete the recruitment. We are constantly facing fears from potential subjects of taking antidepressant treatment during pregnancy.

We have been working with this study for four years, specifying and completing the protocol and getting ethical approval and permission from the national Medical Products Agency. In addition, it has taken an additional year to test the feasibility by completing the first five patients through the pregnancy and delivery parts of the trial (January 2018). During these five years, the multidisciplinary research group with less and more experienced members has had regular meetings. So far, we have not met any problems in raising needed funds, received both from major national and regional funders of clinical research as well as from multiple funders specialized to support studies on safe care of mother and child during pregnancy and in early life. Therefore, we are confident to finish the recruitment within six years, based on our calculations on data from Stockholm Healthcare Region (Figure 2) and publish the results in another three years.

Declarations

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EH and LLG wrote the initial study protocol article with the help of BSS, LF and AF. KW is the principal investigator and JN, LLG, MB and VK are members of the governing study board. MB is the sponsor and the main applicant and receiver of our initial ground-breaking funding decision from the Swedish Research Council. MB is also a senior researcher with full responsibility of the study design and participation in completion of the manuscript.
JN, KW and MB conceived the study protocol and KW wrote the initial draft of the study protocol. EA is developing an exploratory study protocol studying attachment in a subgroup of the pregnant women. MBk, SF and EH launched the open recruitment through different social media platforms. VK and EF adapted the ICBT procedure for use in our pregnant women and are responsible for the ICBT treatment. They also directed the pilot study. AF is the study midwife coordinating the visits and the day to day management of the study. M.B-W, MS and AG are the study psychiatrists responsible for the initial assessment and inclusion in the study as well as for the clinical decisions about pharmacotherapy. E-M.N is the psychiatry nurse responsible for the treatment evaluations. All authors have in different ways been involved in different degrees in the development of study design and take responsibility for the final study design. All authors have contributed to the protocol development and have read and approved the final protocol that we now use after revisions as well as this manuscript. EH and LLG coordinated the completion of the study protocol article.

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Trial Registration and Status

European Clinical Trials Database (EudraCT) Number: 2013-004444-31. Date registered 20140511. Current protocol version 5.3 180507. Recruitment start 2016. Approximate completion of recruitment 2023, approximate completion of data collection 2025.

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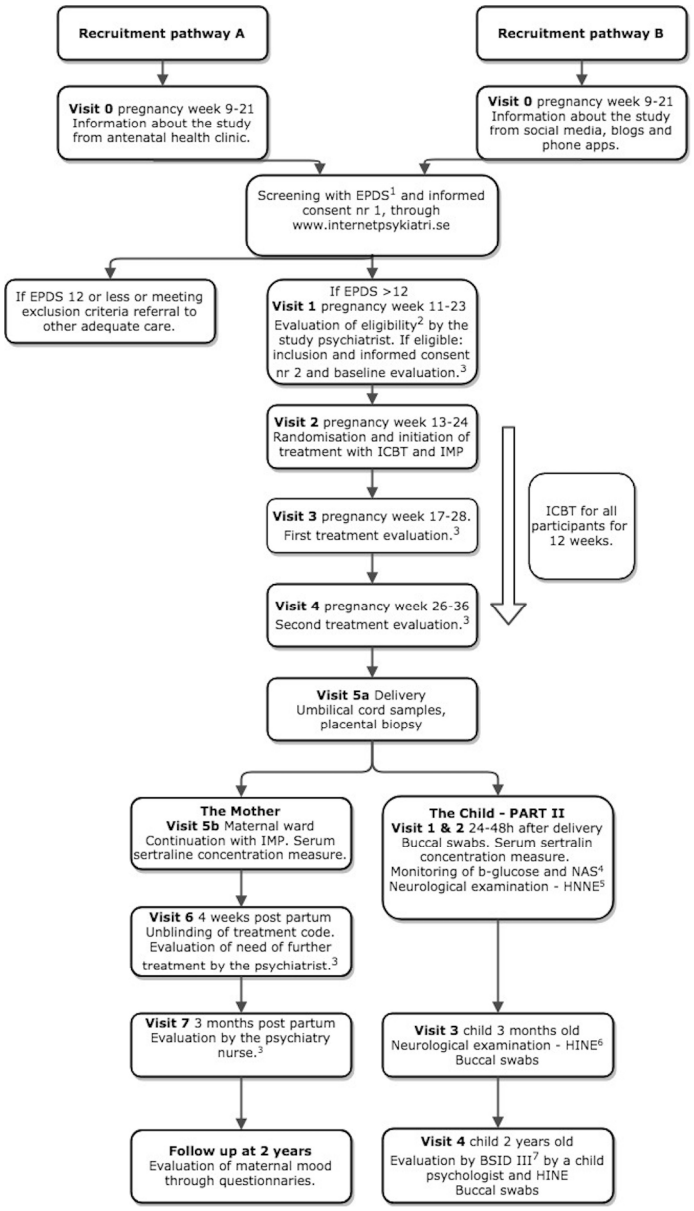

Figure 1. Trial design and participant timeline for the two recruitment pathways. The figure also shows the treatment with placebo/sertraline from visit 2 (pregnancy week 13-24) to visit 6 (4 weeks postpartum) and the ICBT for both groups for 12 weeks, between visit 2 and visit 4 (pregnancy week 26-36) and monitoring of therapy for the two groups. The post-partum follow-up of both mother and child are shown. The different scales and examinations are, as presented in the figure: 1) Edinburgh Postnatal Depression Scale (EPDS)[39], 2) Diagnosis of moderate depression is confirmed according to clinical standard evaluation. Inclusion and exclusion criteria presented in table 1. 3) Evaluation with Montgomery-Åsberg Depression Scale (MADRS)[40], 4) Modified Finnegan Neonatal Abstinence Scale (NAS)[41], 5) Hammersmith Neonatal Neurological Examination (HNNE)[42], 6) Hammersmith Infant Neurological Examination (HINE)[43], 7) Bayley Scales of Infant and Toddler Development III® (BSID III®)[44].

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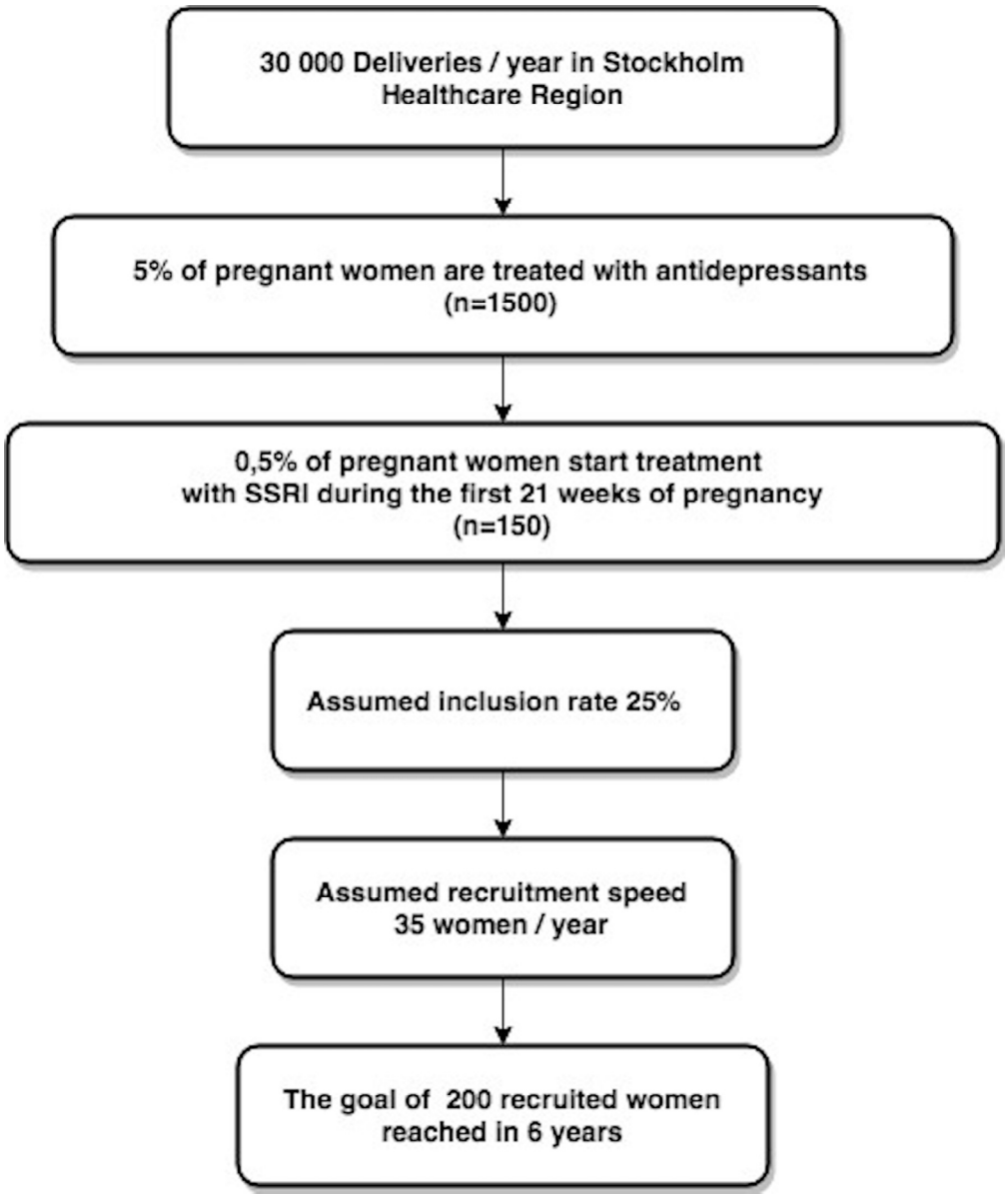

Figure 2. The recruitment base in Stockholm Healthcare Region. Numbers based on an analysis of prescription of SSRI:s in pregnant women in years 2013-2016 in the Stockholm healthcare region with 2,3 million inhabitants. See Acknowledgements.

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EudraCT No: 2013-004444-31

Effects and consequences for mother and child from treatment for depression

A prospective randomised, placebo- controlled, trial with internet-based cognitive behaviour therapy and sertraline or placebo for moderate depression in pregnancy

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Product:	Zoloft® 25 mg
Substance:	Sertraline
Phase of development	*Phase IV*
Protocol number:	*KWMP 001*
EudraCT Number:	*2013-004444-31*
Sponsor:	Mats Blennow, Department of Neonatology, Karolinska University Hospital and Karolinska Institutet (KI)
Coordinating PI:	Katarina Wide, Department of Paediatrics, Karolinska University Hospital and KI
Principal Investigators:	L. L. Gustafsson (Department of Laboratory Medicine, KI), M-L Dahl (Department of Laboratory Medicine, KI), J. Nasiell (CLINTEC, KI) V. Kaldo (Department of Clinical Neuroscience, KI)

Table of Contents

PROTOCOL SUMMARY

PROTOCOL IDENTITY AND OBJECTIVES	
EudraCT Number:	2013-004444-31
Protocol Title:	Effects and consequences for mother and child from treatment for depression. A prospective randomised, placebo-controlled, trial with internet-based cognitive behaviour therapy and sertraline or placebo for moderate depression in pregnancy
Trial Objectives:	**Primary objective** To study the long-term consequences on cognitive development in children exposed to sertraline during pregnancy. **Secondary objective** To study if the effect of ICBT for pregnant women with moderate depression can be increased by adding sertraline **Tertiary objectives** a)To study the direct neonatal effects in children prenatally exposed to maternal sertraline treatment compared to exposure to maternal depression treated with only ICBT. b) To study if add-on treatment with sertraline increases the risk for maternal bleeding and pregnancy complications c) To study pharmacokinetic and genetic variations in the metabolism of sertraline in pregnant women and their children d) To study associations between antenatal maternal depression and inflammatory and epigenetic changes in relation to treatment effects of SSRI in mother and child
INVESTIGATIONAL MEDICINAL PRODUCTS	
Test Product:	Sertraline, 25 mg and placebo
Pharmaceutical Form:	Tablets
Route of Administration:	Orally

METHODOLOGY	
Trial Design:	Prospective, double blind, two armed, parallel clinical study
Dose/Duration:	25 mg, 50 mg, 75 mg, 100 mg and 150 mg for max 33 weeks
Primary Endpoint:	The differences in cognitive development at 2 years evaluated by the standard Bayley Scales of Infant and Toddler Development third edition (BSID-III)®.
Sample Size calculations:	To detect a difference of 7 points (SD 0.5) with a power of 80% (α: 0, 05) in the results in BSID-III. To detect a clinically significant difference, will require a sample of 73 participants in each group. Therefore 100 participants in each group would be appropriate.
Efficacy Parameters:	MADRS-S ,MADRS,EPDS
Safety Parameters:	Adverse events, MADRS- S;MADRS, EPDS
POPULATION OF TRIAL SUBJECTS	
Description of Trial Subjects:	Pregnant women with an untreated moderate depression according to SCID-I.
Number of Subjects:	N=200,receiving treatment with ICBT parallel arms 1:1 N= 100 receive active drug treatment N= 100 placebo
Selection of subjects:	Pregnant women, attending an antenatal clinic and planning to deliver at Karolinska University Hospital or other delivery clinics in Stockholm Healthcare Region which will be added when study is ongoing (path A). The pregnant women can also be recruited via social media and internet (path B).
TRIAL TIMETABLE	
First Subject In:	Q 1 2016
Last Subject In:	Q4 2022
Last Subject Out:	Q4 2024
Study End	Q1 2025
Database lock	Q4 2024
STATISTICAL METHODS	
	Outcome assessments: Descriptive statistics will be assessed on patients' demographics. Adverse events will be reported in proportions in relation to

active/placebo dose. Primary end point will be analysed in multivariate analyses (MVA).

NOTE ABOUT APPENDICES

The appendices to this study protocol (APPENDIX TO MAGDALENA STUDY PROTOCOL PUBLISHED IN BMJ OPEN year:volume:pages) including the informed consent forms are in Swedish. They are available at request from the corresponding author.

Kommenterad [EH1]: Please add the publication details here.

ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse Event
AUDIT	The Alcohol Use Disorder identification test
BSID III®	Bayley Scale of Infant and Toddler Development III ®
CBT	Cognitive Behaviour Therapy
CGI-S	Clinical global impression scale
CRF	Case Report Form
CSQ	Client Satisfaction Questionnaire
DMC	Data Monitoring and Safety Committee
DUDIT	The Drug Use Disorder Identification Test
EPDS	Edinburgh Postnatal Depression scale
EQ-5D	Europe Quality of Life
HINE	Hammersmith Infant Neurology Examination
HNNE	Hammersmith Neonatal Neurology Examination
ICBT	Internet-based Cognitive Behaviour Therapy
IMP	Investigational Medicinal Products
ISI	Insomnia Severity Index
MADRS-S	Montgomery Åsberg Depression (Self-Assessment Scale)
MADRS	Montgomery Åsberg Depression (Evaluator Assessment Scale)
MAMA	Maternal Adjustment and Attitudes scale 12 questions
MPA	Medicinal Product Agency
MPAS	Maternal Postnatal Attachment Scale
NAS	Neonatal Abstinence Score
PAI	Prenatal Attachment Inventory
PSQ	Premenstrual Syndrome Questionnaires
SAE	Serious Adverse Event
SCID-I	Structured Clinical Interview according to DSM-IV R part I
SDQ	Strengths and Difficulties Questionnaire
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCQ	Treatment Credibility Questionnaire

SIGNED AGREEMENT OF THE TRIAL PROTOCOL

Statement of compliance

I have read and understood this protocol version 5.3 dated: 2018-04-06 with the study title***: 'Effects and consequences for mother and child from treatment for depression. A prospective randomised, placebo-controlled trial with internet-based cognitive behaviour therapy and sertraline or placebo for moderate depression in pregnancy.*** I agree to conduct the study accordingly.

Coordinating Principle Investigator
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ALB
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Date 180406

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Date 180406

1 THE DISEASE AND BACKGROUND INFORMATION

Depression occurs in 5-10% of all pregnant women.[1, 2] The prevalence is increased during the pregnant-state compared to the non-pregnant state as well as during the first three months after delivery[1, 3, 4] and can predispose to suicide.[5, 6] In addition, depression increases the risk for preeclampsia and premature delivery.[7] Also a disturbed attachment between mother and child in the new-born period has been reported.[7] Selective serotonin reuptake inhibitors (SSRI) are a class of medicines widely used to treat a number of psychiatric disorders. The Swedish national guidelines to treat pregnant women with moderate depression recommend cognitive behaviour therapy (CBT), interpersonal psychotherapy, or treatment with SSRI.[6] Even though there is substantial evidence supporting the effectiveness of CBT in non-pregnant patients the majority of patients are not treated at all. When medical treatment is used it is usually with SSRI. Only a few studies have assessed the effectiveness of CBT in perinatal depression.[8] In antenatal and postnatal major depression combination treatment with CBT and antidepressants appear to be more effective than antidepressant medication alone, whereas antidepressant therapy alone appears more effective than CBT alone.[9]

An increasingly used alternative to traditional CBT in individual or group format is treatment with a web-based self-help program with active therapist support via the Internet, i.e. internet-based cognitive behaviour therapy (ICBT). The content is not different from regular CBT but is delivered in a different way. ICBT has been shown to be efficient for a range of conditions including depression,[10] with effects comparable to traditional CBT[11] and also producing positive effects when implemented in regular care.[12] The treatment is provided via a secure website where the patients log in to receive the treatment material, usually in the form of separate 'treatment modules' with text and media where the target problem and treatment methods are described and homework assignments are given.[13] The ICBT therapeutic protocol in this study has been modified to pregnant women both in length and in contents.[8] The main function for the therapist is to be supportive and clarify the information, review the progress, give participants feedback, and assist and remind participants not working actively with the treatment. Gradually the therapists guide the participants to access the treatment modules in a specific order. The patient and the therapist work cooperatively with the ICBT components making them relevant in patient's everyday life. Each module, and especially the homework related to the module, is examined by a set of questions. Patients receive feedback from the therapist after each module and also have the opportunity to ask questions when needed. ICBT has been found to be effective in several randomised controlled trials in patients with a long range of psychiatric and medical problems, including moderate depression.[10] ICBT has the potential to be more cost-effective and accessible compared to traditional formats.

1.1 Mood Disorders and Pharmacotherapy During Pregnancy

In clinical practice the standard management of pregnant women with moderate depression is treatment with SSRI. Serotonin crosses the placenta and enters the fetal circulation which can influence the fetal brain. Effects on the developmental process of serotonin on the fetal brain have been shown in animal studies.[14, 15] Effects similar to the 'serotonergic syndrome' observed in adults have been reported in newborns exposed to SSRIs prenatally. These infants display symptoms of jitteriness, irritability, difficulties to maintain body temperature, feeding difficulties and in some cases even seizures.[15] Even though studies have not shown any increased risk for malformations in children exposed to SSRI in fetal life several reports and large registry based studies indicate an increased risk for neonatal complications.[16-20] The SSRI-drug sertraline that is commonly used during pregnancy shows wide variation in plasma concentrations between subjects - up to 15-fold for the same dose in non-pregnant subjects. The concentration of the main demethylated metabolite with limited inhibitor effect on serotonin reuptake exceeds that of sertraline itself. No clear relationship between either effect or

adverse events are demonstrated for sertraline. Data on the disposition of sertraline during pregnancy is limited. Polymorphisms of the sertraline metabolizing enzyme CYP2C19 might explain the variability in drug concentrations between patients.[21] The role of genetic factors for the variability of plasma sertraline concentrations is poorly known in pregnant women as well as the role of the pregnancy itself on drug disposition.

Maternal depression as such may also have an effect on the central nervous system and the autonomic regulation in the new-born infant, induced by physiological changes as increased levels of plasma cortisol. Maternal depression and anxiety seem to inhibit the placental enzyme (11-beta-hydroxysteroid dehydrogenase) activity, causing increased and potentially toxic levels of cortisol in the fetus.[22] Furthermore, epigenetic mechanisms such as DNA methylation of cortisol, glucocorticoid and serotonin receptors and their pathways may be involved.
Also telomere biology may be involved in increased vulnerability to disease in the infant.[17] Epigenetic changes with reduced telomere length in leucocytes have been shown in patients with depression. Pre- and perinatal stressors in children have also been shown to effect telomere length.[22-24] Epigenetic changes in depression may be related to inflammatory and hormonal factors and seem to be reversible by treatment.[25]
Maternal stress factors may therefore contribute to changed neurotransmission in the developing fetal brain. Data on the long-term consequences of the unborn child's cognitive development after prenatal exposure to SSRI and/or maternal stress are scarce. Only a few studies using small study samples have been published.[26-31]

2 TRIAL RATIONALE

The etiology of depression during pregnancy is unknown. Pregnancy-related physical and hormonal changes as well as psychosocial stressors might render women vulnerable for stress activation. Despite lack of scientific evidence for pharmacological and psychological treatment of antepartum moderate depression, CBT is recommended as first choice treatment (The National Board of Health and Welfare, National guideline for Depression). CBT is generally less available and as a consequence the majority of pregnant women with moderate depression are not treated at all. The ones who receive treatment are recommended SSRI. International meta-analyses suggest greater effect when combining traditional psychological and pharmacotherapy. To our knowledge no prior placebo-controlled clinical trials have assessed if combination treatment is superior to treatment with internet-based CBT alone. Research concerning physiological and psychological factors that negatively influence the unborn child and maternal well-being are crucial to investigate.

This study targets women with moderate depression during pregnancy. We will use ICBT with or without SSRI in a randomised placebo-controlled trial. This study can help to fill the gap of knowledge on the consequences of antidepressive therapy for the children as well as in field of maternal treatment of depression. The study is divided into two parts 1) The pregnant women with moderate depression and 2) the children born to the women with moderate depression. Our research group has worked extensively with ICBT and has a large experience and publications of this treatment.

The **overall aim** is to study the neonatal effects and the long-term consequences on cognitive development in children exposed to sertraline for maternal depression during pregnancy. We also seek to optimize the treatment of depression in pregnant women by comparing the add-on efficacy and

safety of a combination of internet-based cognitive behaviour therapy (ICBT) and SSRI-treatment with ICBT-therapy alone.

3 OBJECTIVES

3.1 Primary Objective

The primary objective is to study the long-term consequences on cognitive development in children prenatally exposed to maternal sertraline treatment compared to exposure to maternal depression treated with only ICBT.

3.2 Secondary Objective

The secondary objective is to evaluate the safety and the efficacy of sertraline in addition to treatment with ICBT.

3.3 Tertiary Objectives

These include:

a) To study the direct neonatal effects in children prenatally exposed to maternal sertraline treatment compared to exposure to maternal depression treated with only ICBT.
b) To study if add-on treatment with sertraline increases the risk for maternal bleeding and pregnancy complications.
c) To study pharmacokinetic and genetic variations in the metabolism of sertraline in pregnant women and their children.
d) To study associations between antenatal maternal depression and inflammatory, epigenetic and telomere biology changes in relation to treatment effects of SSRI in mother and child.

4 ENDPOINTS

4.1 Primary Endpoint

Cognitive development at 2 years of age evaluated by the standard Bayley Scales of Infant and Toddler Development v 3 (BSID-III) in children exposed to maternal treatment with ICBT and sertraline compared to exposure to ICBT only.

4.2 Secondary Endpoint

Add-on effect of sertraline measured in difference i) in self-report of depressive symptoms (MADRS-S), ii) in rate of remission from depression (measured by diagnostic psychiatric interview with MADRS at 12 weeks, 14 weeks, and 30 weeks (= 3 months postpartum) of treatment.

4.3 Tertiary Endpoints

These are the exploratory parts of the study.

a) To study the neonatal effects in children exposed to sertraline during pregnancy
   - Differences in admission rates to neonatal care units will be compared between groups. Infant motor behaviour examined with standardized methods (HNNE) and neonatal abstinence effects are scored with NAS.

b) To study if add-on treatment with sertraline increases the risk for maternal bleeding and pregnancy complications
   - Evaluation of the risk for maternal postpartum bleeding in ml and postpartum haemoglobin day 2. APTT/TPK and placenta biopsy for evaluation of genetic differences in activity of 11-beta-hydroxysteroid dehydrogenase type 2 and in pharmacological metabolism, DNA methylation for telomere length and telomerase activity.

   - Evaluation of the risk for the pregnancy complications preeclampsia, placental abruption and increased caesarean section rate.

c) To study pharmacokinetic and genetic variations in the metabolism of sertraline in pregnant women and their children
   - Plasma concentrations of sertraline and genetic variations in the metabolism of sertraline, genetic variants of metabolizing enzymes/transporters. The pharmacological and pharmacokinetic assessments include: plasma sertraline concentrations, effects of various genetic variants controlling drug metabolising and drug transporters on sertraline disposition and metabolism. Exploration of relationship between plasma sertraline concentrations and prolactin levels.

d) To study associations between antenatal maternal depression and inflammatory and epigenetic changes in relation to treatment effects of SSRI in mother and child
   - Effects on levels of s-hCG and cytokines. Telomerase activity through the umbilical vein and buccal swabs for analysis of epigenetic variables and telomere biology. Epigenetic and telomere biology assessments: DNA methylation, telomere length and telomerase activity

5 DESIGN

5.1 Outline

This is a prospective, randomised, placebo-controlled, double blind, two parallel, single centre clinical investigation of pregnant women with moderate depression with multiple delivery units. The subjects will visit the centre approximately 6 times during a period of 13 months from early-mid pregnancy until two years after delivery. The patients are recruited via two paths; (A) from the antenatal clinics in Stockholm Healthcare Region (2,3 million people) and (B) via a direct application and screening on the internet, where an initial telephone interview is used for screening, to ensure they have contact with regular antenatal care and to book an appointment with a psychiatrist.

All subjects will be consented before any study-specific procedures and assessed for eligibility within three to five weeks and consented for treatment one week before treatment start. The screening period in regular care (path A) starts when the pregnant women attend the antenatal clinic (pregnancy week 9-21). They will obtain written and oral information about the study through their attending midwife and are asked to fill in the Edinburgh Postnatal Depression Scale (EPDS) to screen for potential depressive disorder. Women will be informed that they at this stage only consent to participate in screening and if the screening is positive to be contacted for psychiatric assessment (verbal informed consent #1, which covers only the initial, non-pharmacological, part of the study). They will receive information about how to assess the internet-based screening questionnaires (MADRS-S, STAI, AUDIT, DUDIT, EQ5D, ISI), questions on previous somatic and psychiatric health issues, sociodemographic factors and questions on perceived health of the participant's partner. Before completing these forms, they have to read and agree to the written informed consent #1. Women screening positive for potential depression (EPDS >12 points) will be contacted by a research nurse specialized in psychiatry for a second evaluation of eligibility and scheduled for a visit to the study psychiatrist. The optimal cut-off score on the EPDS scale for screening purposes is 13 or more points (standard error coefficient of 1.09 and c-statistics of 0.84) which have been shown to give 77% sensitivity.[32]

Women recruited directly via internet (path B) will start by completing a slightly modified version of the written informed consent #1 and then complete the same internet-based screening questionnaires, with some additional questions. Women are then contacted via telephone for further screening, including all questions asked at the antenatal clinic in recruitment path A and confirming that they are receiving regular maternal care. Women not suitable for inclusion are referred to regular health care services if needed. Eligible women are booked for a time to visit the psychiatrist.
After assessment and information about the study by the study psychiatrist, the women will sign an informed consent (informed consent #2, covering the rest of the study). Treatment with ICBT and randomised treatment with either active treatment with sertraline or placebo will start after the internet-based screening questionnaires have been completed in conjunction with a visit to the study centre approximately one week later. Women uncertain about participation at the time of psychiatric assessment are offered to discuss with the study obstetrician when visiting the study centre one week later where they can provide informed consent (informed consent #2).
The research nurse in psychiatry or the research midwife will make a telephone call within 1 week after the first visit to schedule an appointment at the study site and address any difficulties to assess the internet treatment platform.
Once included the patients will have scheduled visits to the specialists' antenatal clinic at Karolinska University Hospital Huddinge or at other participating centres to measure vital signs, blood sample collection, accountability of IMP and adverse event report. The last visit is performed 12 weeks after delivery.
When starting ICBT by logging in on the internet-treatment platform after randomisation, pre-treatment self-report measures will be completed (MADRS-S, STAI-s, ISI, EQ5D, Life Events, PSQ, PAI, MAMA). At the follow-up after the delivery the women are asked to complete the MPAS, ISI, TCQ, client satisfactory questionnaire, questions on adverse events (AE), questionnaires on basic socio-demographic data and health as well as questions on how they experience the psychiatric status of their partner. This last questionnaire will be repeated 3 months after the delivery. During the 12-week internet-CBT treatment patients self-assess symptoms weekly with MADRS-S. Post ICBT-treatment (week 12), week 14 and week 30 self-reports are also completed online.

A psychologist and a research nurse specialized in psychiatry will work closely together with a psychiatrist to assess the best psychiatric and safety management of the patients. The psychologist supervises and monitors each patient individually on a weekly basis during the 12 weeks of ICBT for an

early detection of symptoms that indicate disease progress or improvement. Any symptoms that require further expertise and support by a psychiatrist will be considered. The psychiatrist will consider all aspects of the patients' well-being in a detailed assessment rating the strength of clinical evidence of stressors and psychiatric status and level of functioning at each visit to the clinic.

All visits to the study psychiatrist and interaction with the unit for Internet Psychiatry are documented in health care journals (Take Care® or Obstetrics®) or systems used on site according to routines and practices at the psychiatric services for Stockholm Healthcare Region and Karolinska University Hospital and at additional study sites.

5.2 Selection of Subjects

Inclusion Criteria (all of the below)

1. Female > 18 years old
2. Pregnant, gestational week 9-21
3. Verified moderate depression according to SCID-I with or without concomitant anxiety disorder.
4. Signed informed consent
5. Able to understand the Swedish language orally and in written, write in Swedish and able to use the internet for the ICBT, including having succeeded in filling out online questionnaires.
6. Are willing to participate to all study visits
7. Plans to give birth at the Department of Obstetrics at Karolinska University Hospital, Huddinge or other delivery units within Stockholm Healthcare Region.

Exclusion Criteria (any of the below)

1. Known drug or alcohol abuse
2. Serious psychiatric disorder such as psychosis, bipolar disorder, severe personality disorder, ADHD/ADD with diagnosis and symptoms in adult age, autism, mental retardation and severe melancholic or psychotic depression.
3. Known idiosyncrasy to sertraline (Zoloft^{R}) or allergy to any of excipients in the Zoloft product
4. Ongoing drug therapy with antidepressants, mood-stabilizers, central stimulants, antiepileptic drugs, opiates, insulin, oral anti-diabetics, antiarrhythmics or steroids.
5. Any severe somatic disease that necessitates regular treatment with systemic steroids, severe heart and lung disease, kidney disease, liver disease, diabetes mellitus or epilepsy with drug treatment.
6. Women who either during screening or treatment on self-assessment forms (MADRS-S: 4 or more points on question about suicidal intention (question 9)) report symptoms of severe suicidal thoughts or suicide plans will be contacted for structured suicide risk assessment by telephone according to clinical routine at the unit for internet psychiatry. If judged necessary patients will be booked for psychiatric assessment by the study nurse. If urgent assessment or care is judged necessary, referral to psychiatric emergency departments will be made according to the same routine as in regular care.
   Also women, who contact the study personnel and report symptoms of suicidal thoughts or suicide plans will receive psychiatric assessment as specified above. Women who according to psychiatric assessment have a high suicidal risk will be excluded from the study. These women will be actively transferred into necessary psychiatric treatment as usual.

7. Other factors that are clinically significant and could jeopardize study results or its intention, as judged by study psychiatrist or study obstetrician.

5.3 Recruitment Base

Concerning recruitment path A (via regular maternal care), with an estimated number of 30 000 annual deliveries in the Stockholm Healthcare Region and an estimated rate of depression among pregnant women of 5%, we expect 1500 pregnant women with depression in the catchment area. We estimate 0,5%, 150 patients, starting treatment with SSRI during the first 21 weeks of pregnancy. An inclusion rate estimated to 1/4 results in recruiting 35 pregnant women/year for the study. The alternative recruitment path (B), via media and internet, will be used to increase the speed of inclusion.
Since many years there is a special outpatient clinic for pregnant women with depression or anxiety at Karolinska University Hospital, Huddinge. The clinic is a joint venture between the Department of Obstetrics and Gynaecology and the Department of Psychiatry in Stockholm Healthcare Region.

6 ASSESSMENTS AND PROCEDURES

6.1 Visit 0 (Day -28 +-7days weeks before start of treatment) 'Informed Consent'# 1

Pregnant patients planning to deliver at Karolinska University Hospital Huddinge or other delivery units within Stockholm Healthcare Region. They should be pregnant approximately in **gestational week 9-21** will be informed about the study during a regular visit to their antenatal health clinic by their attending midwife (recruitment path A). All these women (except those as specified in the exclusion criteria, see section 5.2 for details) will receive oral and written information about the nature of the trial by their attending midwife and agree to participate in the first part of the study (oral informed consent #1).
At this stage, they will only agree to participation to screening and, if being screened positive, to complete more screening questionnaires via the internet and perform a visit for a diagnostic and clinical assessment by a psychiatrist. After the oral informed consent patients will be asked to complete the Edinburgh Postnatal Depression Scale (EPDS) to screen for potential depressive disorder. The written information about the trial will contain a description of the internet-CBT treatment and how to log on to the internet platform www.internetpsykiatri.se, where they will choose their personal password and register their mobile phone number to which they will get a text message with a temporary code for each time they log on to the internet platform. The EPDS will be collected and evaluated by the research midwife on a weekly basis. Women scoring >12p will be encouraged to obtain the login at www.internetpsykiatri.se if they agree to participation in the study.
Through www.internetpsykiatri.se the women will log in to the internet platform at the Internet Psychiatry Unit at Psychiatry Southwest, used to administer web-based questionnaires and to later deliver ICBT. The advantage of the electronic system is that it can be accessed and used by patients from geographically different locations. On the internet platform they will complete the written informed consent #1 and then be asked to deliver information about their choice of delivery hospital, current drug therapy, current mental and somatic disorders, questions on perinatal current and previous somatic and mental symptoms. They are also to answer questions on perceived health of the participant's partner, practical questions on ability and suitability to take part in the study, and fill out the established self-report questionnaires PAI, AUDIT, DUDIT, MADRS-S, ISI, STAI, EQ5D, questionnaire on parity, number of children, country of birth and sociodemographic background. This will take about 30-45 minutes.

There is also a direct way to apply for participation in the study (recruitment path B). Here, women find information about the study in articles or advertisement in media or on the internet, and if interested they find more information at www.magdalenastudien.se from where they are guided to the alternative screening questionnaire at www.internetpsykiatri.se. This starts by completion of a slightly adapted version of the written informed consent #1, followed by the same internet-based screening-questionnaires, with the following added; EPDS, contact details, and questions about gestational week, pharmacological treatments, somatic conditions, language skills, computer skills, internet availability, age, current maternal care/clinic, and if they can accept having their delivery at the most nearby study centre. This will take about 40 to 60 minutes.

6.2 Phone contact (Day -21 days +- 14 days before start of treatment) 'Nurse follow-up'

Patients are now in gestational week 10-22. For women recruited via path A, the research nurse in psychiatry or the research midwife will contact the women who have screened positive (EPDS >12 points). The reason for this call is to do a new clinical assessment on the woman's health situation, to give the woman possibility to address questions about the study, and to check whether they were able to obtain log-in for the internet-CBT platform at www.internetpsykiatri.se. The women will be reminded to use the web-based self-assessment instruments if they have not already done that and are informed about the scheduled visit to the psychiatrist. More phone calls and text messages will be used to remind the women to fill out the web-based questionnaires.
All women recruited via path B will be contacted via telephone when they have completed all internet questionnaires, for further information but also for further screening. The EPDS and all the inclusion criteria checked at the antenatal clinic in recruitment path A will be cross-checked. Eligible women are informed about the first scheduled visit to the psychiatrist.

Regardless of recruitment path, women with EPDS >12 points but not eligible according to inclusion and exclusion criteria will be offered to receive referral for psychiatric assessment. The research midwife/ research psychiatric nurse will contact the woman's attending midwife and inform them where to refer the patient for further psychiatric assessment. The midwives keep a screening log of all subjects that have performed screening and will document in the screening log patients that decline further participation.
Women reporting more than 2 points on the EPDS question on suicidality or 4 or more points on the suicidality item in MADRS-S will be contacted by phone by a psychiatric nurse for a structured telephone suicide assessment. If needed, the women are referred to the appropriate level of care based on evaluation by the psychiatrist.

6.3 Visit 1 (Day-14 +- 7days before start of IMP) 'Psychiatrist, Informed Consent #2'

Patients are now in gestational week 11-23. Visit to perinatal psychiatrist at the specialist antenatal health clinic, Karolinska University Hospital Huddinge or at other study sites in Stockholm Healthcare Region. The psychiatrist will perform a clinical psychiatric assessment and evaluate the women with the Computerized Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and Clinical Global Impression Scale (CGI-S) to evaluate general symptom severity and MADRS. The women who fulfil criteria for moderate depression according to SCID-I and have no exclusion criteria will be asked to sign the informed consent #2 on the treatment with ICBT and the randomised controlled trial with treatment with sertraline or placebo.
The women who have failed to complete the web-screening are informed that this is at requirement for participation in the study. They will receive more guidance and hands-on-help in how to log in to www.internetpsykiatri.se if necessary.

Women uncertain about participation at the time of psychiatric assessment or women who have not yet completed necessary web-screening are offered to discuss with the study obstetrician when visiting the study centre one week later when they can provide informed consent (informed consent #2).
All study participants will be documented in an inclusion log. Those not consenting to participate or not fulfilling criteria for moderate depression in the study are offered treatment as usual and will be documented in the screening log as screening failure.

Please note! Patients who are assessed having a high suicide risk will be excluded from further participation in the study and will recorded as 'screening failure'. They will be referred to a psychiatric clinic for further evaluation and treatment according to clinical routines.

6.4 Phone contact (Day -4 days +- 2 before start of treatment) 'Nurse follow-up'

Patients are now in gestational week 12-25. All patients who visited the psychiatrist and confirmed further participation in the study will be contacted by the study midwife. The reason for this call is to give the women the possibility to address questions about the study and to check whether they were able to obtain log-in for the internet-CBT platform (electronic identification and log in to the account at 'My health care contacts'). Women not having been able to fill out the web-screening are informed that this is a required for participation in the study. If necessary, more guidance in how to log in to www.internetpsykiatri.se is given.
Women who were uncertain about participation at the time of psychiatric assessment and who want further information for decision to participate in the study are scheduled for a visit to the study obstetrician. This visit is scheduled to the study centre one week later where they can provide informed consent (informed consent #2).
Women are scheduled for a visit to the antenatal clinic within the following week (research midwife). Patients are instructed to be fasting from midnight.

6.5 Visit 2 (Day 0 Start of treatment), 'Baseline, Randomisation & Treatment Start'

Patients are now in gestational week 13-26. Visit at study site.
The investigator will review inclusion criteria, concomitant medication and fill in the 'Eligibility Form' in the CRF. If eligible with a completed web-screening, patients will be randomised according to standard procedures. This will be stated also in patients' medical record (randomisation number, storage of coded envelopes etc.). This means that only patients who are able to use the website www.internetpsykiatri.se are eligible to participate in the study as specified in inclusion criteria 5. Patients that have not completed the internet questionnaire at this point might be given the opportunity to do so if the time permits and if it is possible to schedule a new meeting with the research midwife to continue Visit 2.

Any adverse events will be actively asked for and documented. The following blood samples will be collected: for endocrinological (TSH, prolactin), inflammatory (cytokines), and basic blood parameter analyses (Hb, MCV, MCHC), APTT as well as for epigenetic and telomere biology variables (leucocytes for telomere length, telomerase activity (RNA), DNA methylation), and DNA to study genetic differences in activities of drug metabolizing enzymes and drug transporters. The total volume of blood for the whole study period is 200ml. All blood samples except for haemoglobin and thyroid hormones will be frozen and analysed later. Haemoglobin and thyroid hormones will be analysed. Cell separation will be performed within 6 hours for the blood samples for epigenetic variables and telomere biology.
If the haemoglobin or thyroid hormone concentrations are impaired the women will receive regular treatment according to standard procedures. Further, vital signs (height, weight, pulse and blood pressure) for 'baseline' evaluation will be measured. The patients are instructed to store the investigational medical product (IMP) as instructed and carefully follow the dosing scheme.

The patients will receive a 'subject diary' with contact details of involved staff and information regarding each of the following visit. There they will find written instructions on how to report and who to call if acute psychiatric services are required. This subject information also includes contact details on who to call if thoughts or feelings become overwhelming. The subject diary will be available as a document in the internet platform for the ICBT.

After the visit, the research midwife contacts the coordinator of the internet treatment to inform them that the patient is about to start treatment. The coordinator decides on a therapist that will contact the patient to present themselves, give some basic information about the internet treatment and answer question that concerns the internet treatment.

Please note! All subjects are informed that in any emergency situation, they should phone the Swedish Emergency Number 112 and/or visit the emergency department as in usual care. The code for the study drug can be broken at any time if necessary by the principal investigator or by any of the physicians to whom the principal investigator has delegated the responsibility.

Support and supervision regarding the ability to use the treatment platform for the ICBT is performed on site. Internet psychiatric treatment will be started at the same time as the pharmacological treatment and will continue for 12 weeks. The PRE-measurement in conjunction with start of ICBT treatment include: Women will be asked to complete the web-based self-assessment instruments in the pre-treatment assessment: MADRS-S, STAI-S, EQ5D, Life Events, PSQ, PAI, ISI, EPDS

During the internet treatment the women will self-assess their symptoms weekly with MADRS-S.
At treatment day 24-34 (week 4) self-assessment with EQ5D, PAI, and ISI will be performed via internet, together with questions on how the patients perceive and use the internet treatment and the drug treatment, including adverse events (and their perceived relation to each treatment). A question if they believe they have received the active drug or the placebo will be administered to act as a blinding control. Also, two versions of the Treatment Credibility Questionnaire (TCQ), one each for the ICBT part and the pharmacological part of treatment respectively will be administered. These instruments will also be administered at week 2.

6.6 Visit 3 (week 4 +- 6 days) 'First Treatment Evaluation'

Patients are now in gestational week 17-30. Patients will have telephone contact or visit the site for consultation and for clinical assessment by the research nurse in psychiatry. At this visit also safety and effect assessments, CGI-S and MADRS will be carried out. If the extra internet-measures at treatment week 4 have not been filled in, the participant is encouraged to log in and do this at the site. The midwife/research nurse in psychiatry makes an 'Accountability log' on the IMP returned to site and controls for any perceived adverse events. If the patient according to diagnostic assessment with MADRS still fulfils criteria for moderate depression, the research nurse in psychiatry contacts the psychiatrist for increasing the dose of IMP or placebo. In these cases the patients have to collect a new container with an increased amount of tablets and return the previous one to the research midwife.

Blood sample collection to measure the following parameters will be collected: prolactin, full blood count, plasma sertraline serum concentration will be collected. Basic parameters (weight, pulse, blood pressure) and concomitant medication will be measured and documented.

Post-treatment self-assessment after ICBT (gestational week 27-38)
The ICBT will be terminated after 12 weeks (in gestational week 27-38). Patients will fill in internet self-assessments (POST) at the end of the ICBT (see below, visit 4), where they also report adverse events.

6.7 Visit 4 (week 14 +- 6 days) 'Second Treatment Evaluation'

Patients are now in gestational week 26-39. Patients will have telephone contact or visit the site for consultation for clinical assessment by the research nurse in psychiatry, and also safety and effect assessments, CGI-S and MADRS will be completed. The midwife or the research nurse in psychiatry makes an 'Accountability log' and controls for experienced adverse events. If the post-treatment internet self-assessment has not already been completed, the women will be asked to use the internet platform to self-assess with MADRS-S, STAI-s, EQ-5D, ISI, adverse events, satisfaction with treatment (CSQ) including additional questions on how the patients perceive and use the internet treatment and the drug treatment, blinding control and PAI. At the end of the treatment, the ICBT-therapist will also make a short, structured rating of the participant's compliance to the ICBT manual. Blood sample collection for the following parameters: prolactin, HCG, inflammatory, sertraline plasma concentration, full blood count and epigenetic and telomere biology variable. Vital signs and concomitant medication will be documented.
If the woman according to psychiatric assessment with MADRS-S still fulfils criteria for moderate depression, the research nurse in psychiatry contacts the psychiatrist for increasing the dose of the IMP. In these cases the patients have to collect a new container with an increased amount of tablets and return the previous to the research midwife.

6.8 Visit 5 (week 18 +- 6 days) 'At Delivery'

NOTE: Part II of the study, Follow up of the infants born to study mothers, begins at the same time. (See paragraph 6.11.)
Patients are now in gestational week 40 or in labour, at delivery unit.
At the previous visit the research nurse has noted in the computerized medical record Obstetrix®
that the following blood samples will be collected at the delivery:
From umbilical cord from the infant to measure: plasma concentration of sertraline, genetic variants for controlling activity of enzymes regulating the metabolism of sertraline, epigenetic and telomere biology variables in leucocytes.
From the woman: a placental biopsy to measure 11-beta hydroxyl steroid dehydrogenase type 2 and for epigenetic and telomere biology analyses in placenta.
In the maternity ward the following morning after delivery: full blood count, prolactin, plasma concentration of sertraline. The maternal blood loss during delivery and infant Apgar points are documented in CRF and in the medical record (Obstetrix®).
The midwife will schedule a visit to the antenatal clinic within a 4 weeks period including a visit to the psychiatrist.
The women are instructed to continue their dose of IMP as prescribed.
The women are informed that they will be observed in the hospital for at least 48 hours after delivery.
See paragraph 6.11 for the evaluation of the infants!

6.9 Visit 6 (week +22 +- 6 days) 'Four weeks after Delivery'

Visit at site. Patients will visit the site for clinical assessment by the psychiatrist, and for safety and effect assessments with CGI-S, EPDS and MADRS. The midwife makes an 'Accountability log' on drugs returned to site and controls for adverse events.

Self-assessment rating scales have already been filled out on the internet before the visit including EQ5D, MAMA, questions of breast feeding, MADRS-S, MPAS and ISI. Blood sample collection on the following: prolactin, inflammatory parameters, full blood count and a sample for measurement of sertraline plasma concentrations.

The blinded phase of the study is now terminated and the treatment is revealed for the women and the psychiatrist. Note that all study staff except for the psychiatrist and the psychiatry nurse will remain blinded through all forthcoming visits and analyses. Women on active treatment with sertraline will be recommended to continue treatment. Women treated with placebo and showing signs of clinical depression will be recommended treatment with sertraline according to clinical routine until one year after delivery.
Patients' self-assessment questionnaires should have been filled in via internet before the visit: MADRS-S, EPDS, EQ-5D, ISI, MAMA, MPAS adverse events and questions about breastfeeding. Blood sample collection for concentration of sertraline.

The midwife makes an 'Accountability log' on drugs returned to site and controls for adverse events.

6.10 Visit 7 (week + 30 +- 2 weeks) '3 months after Delivery'

Visit at site. Patients will visit the site for consultation for clinical assessment by the research nurse in Psychiatry including safety and effect assessments, CGI-S and SCID-I (only depression module) at the same time as visit 3 for the child (paragraph 6.13).

PART II: THE CHILD BORN TO A MOTHER IN THE STUDY

6.11 Visit 1 (+24 hours to 48h after delivery) Study paediatrician

The women are informed that they will be observed in the hospital for at least 48 hours after the delivery.

Clinical and neurological examination by the study paediatrician according to the standardized protocol Hammersmith Neonatal Neurological Examination (HNNE) will be performed once within 48h of age. Buccal swabs are used for sampling of DNA for assessment of epigenetic, pharmacogenetic and telomere biology variables.

The following blood samples will be collected: Capillary plasma glucose levels on infant before the 2nd meal (5-10 µl).
Neonatal abstinence score (NAS) will be evaluated every 8 hours by the midwife/nurse at the maternity ward between 24 to 48 hours of age and longer if necessary.

6.12 Visit 2 (+ 48 hours after delivery) Study paediatrician

The following blood samples will be collected: for plasma glucose (5-10 µl) and for measurement of plasma concentrations of sertraline (500µl) .The blood sample will be collected at the same time as the routine neonatal screening.

6.13 Visit 3 (child at three months of age) Study paediatrician and 'Nurse follow-up'= Visit 7 for the women

Clinical and neurological examination by study paediatrician with Hammersmith infant Neurological Examination (HINE). Data on body measurements are extracted from the Child Health Clinics electronic documentations. Buccal swabs are used to sample DNA for assessment of epigenetic and telomere biology variables.

Parental attachment, maternal health and questionnaires about psychiatric status of the partner and breast feeding is recorded in the questionnaires completed online, described under visit 7 in the maternal part of the study (paragraph 6.10).

6.14 Visit 4 (child at two years of age) to child psychologist and study paediatrician

A child psychologist will perform the evaluation with Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®). The study paediatrician will use HINE for evaluation. Buccal swabs are used for sampling of buccal tissues containing DNA for assessment of epigenetic and telomere biology variables will be taken. The women will complete the following questionnaires: MAMA, MPAS, Maternal psycho-social status, SDQ, MADRS-S. Furthermore growth charts from child health clinics will be collected from the electronic medical record system.

The visit at 2 years of age is the last visit in this part of the study. We are planning a follow up of the children at 5.5-6 years of age with evaluation by a child psychologist and questionnaires on development and behaviour. A detailed study protocol for this will be developed when this third part of the study will take place.

7 WITHDRAWAL OF SUBJECTS

7.1 Criteria for Withdrawal

Subjects are free to discontinue their participation in the study at any time and for whatever reason without explanations. If possible, the reason for withdrawal of consent should be documented. The subjects may be discontinued from study medication at any time at the discretion of the investigator(-s). The reason to discontinue subjects from study medication (other than exclusion criteria) could be:
Subject is lost to follow up
Severe protocol violation
Severe adverse events (SAE) e.g. patients that according to psychiatric assessment have high suicidal risk, allergic reactions.
Intercurrent illness violating the conditions of the study.

8 TREATMENT

8.1 Description of Investigational Medicinal Products (IMP)

The investigational medicinal product (IMP) is a capsule containing either sertraline hydrochloride or placebo manufactured by APL (Apoteket Produktion & Laboratorier AB, Stockholm, Sweden). The capsules of active drug are made of hard gelatine and filled with sertraline hydrochloride corresponding

to 25mg sertraline using Zoloft® (25mg sertraline film-coated tablets, Pfizer Ltd, New York) and with a microcrystalline cellulose filler. The placebo capsules are made of identical microcrystalline cellulose filler embedded into an identical hard gelatine capsule. The IMP is delivered by the producer in sealed HD polyethylene containers, labelled according to a randomisation list. Patients are randomised to treatment by Karolinska Trial Alliance (KTA) with block randomisation. The size of these blocks is blinded for the investigators.

Treatment with sertraline/placebo starts with titration of 25 mg (1 tablet) daily for 5 days, and increases to 50 mg daily (2 tablets) until first treatment evaluation. After the first treatment evaluation the dose can be increased to 100 mg daily (4 tablets) with titration of 75mg for 5 days. After the second treatment evaluation the dose can be increased further to a maximum 150 mg/day (without titration). Any change of dose of IMP will only be performed after the psychiatrist's evaluation of the patient's safety and effect. Patients are not allowed to titrate the dose by themselves, not even after telephone consultation with the psychiatrist. The IMP can be administered either with or without food. If the patient notices signs of deterioration she is instructed to contact the research nurse by phone or in acute cases the psychiatric emergency department. The research nurse can then contact the psychiatrist for discussion, or in acute cases, she can directly contact the psychiatric emergency department. If necessary, the psychiatrist can call the patient and either refer her for acute psychiatric assessment or book the patient in for an extra visit.

8.2 Treatment Assignment

Patients will be randomly allocated to the next consecutive patient number when the investigator has verified that the patient fulfils the eligibility criteria.

8.3 Blinding and Code Breaking

This is a double-blind trial. Blinding will be accomplished by ensuring that the active substance and placebo are of identical appearance and packaging. The treatment code will be broken at one month after delivery or earlier for safety reasons judged by the investigator. Coded envelopes and code lists will be locked in a cupboard at the Pharmacy at Karolinska University Hospital, Huddinge. If a patient pre-terminates the study the date and the reason for withdrawal is documented in the CRF. The same procedure will take place at additional study sites. There is also an external Data Monitoring and Safety Committee (DMC) who can in due cases break the treatment code. The DMC will have senior expertise in clinical pharmacology (paediatric focus), neonatology/paediatrics, psychiatry and biostatistics.

9 ALLOCATION TO TREATMENT

The patients receive verbal and written instructions on how to use and store the IMP.

9.1 Prior and Concomitant Medication

Relevant medication history (prior medications) as judged by the Investigator will be documented in the CRF. At each visit the investigator (or his/hers designee) will ask for concomitant medication. During the study period concomitant use of the following drugs may be needed in either study group: Regular use of promethazine or propiomazine. Oxazepam in case of severe anxiety on rare occasions. These concomitant medications will be reported.

1. ASA
2. NSAID
3. Oxazepam/Promethazine
4. Propiomazine

.

9.2 Compliance to Treatment & Product Accountability

All patients should administer the IMP as instructed. The research nurse will make accountability checks and document any discrepancies found. The monitor will also make an accountability check and document any compliance issues. At the end of the ICBT, the ICBT-therapist will also make a short, structured rating of the participant's compliance to the ICBT manual.

9.3 Continuation of Treatment

All patients should administer the IMP once daily from the randomisation visit until visit 6 (4 weeks after delivery). All patients in the active treatment arm will be offered continuation of the treatment as in routine care.

10 ASSESSMENT OF EFFICACY AND SAFETY

10.1 Clinical Safety Assessments

To evaluate the efficacy and safety of combined treatment with ICBT and sertraline vs. ICBT alone for antenatal moderate depression

Evaluation of efficacy:

a) Effect size of the add-on effect of sertraline measured in difference in self-report of depressive symptoms (MADRS-S) at 1-12 weeks, at 14 weeks, and at 22 weeks (4 weeks postpartum) of treatment. All self-reported assessment are performed online.
b) Add-on treatment effect of sertraline measured in rate of remission from depression (measured by diagnostic psychiatric interview MADRS at 4 weeks, 14 weeks and 22 weeks (4 weeks postpartum) of treatment.
c) Effect size of treatment effect of ICBT calculated as difference of self-report of symptom (MADRS-S) pre- and post-treatment.
d) Risk of suicidality measured as change from baseline (measured by MADRS-S and MADRS) and as occurrence of exclusion during the study due to psychiatric assessment of high suicidal risk

Evaluation of safety:

The psychologist and the psychiatrist work in collaboration to ensure that patients are ensured optimal psychiatric care and safety. The psychologist supervises and monitors each patient individually on a weekly basis online, for an early detection of symptoms that indicate 'disease progress' /'disease improvement' and any symptoms that require further expertise and support by a psychiatrist. The psychiatrist has the main responsibility to clinically decide about inclusion of patients and to monitor the efficacy and safety of treatment with help of psychiatric nurse. The psychiatrist recommends the PI if a patient needs to withdraw from the study due to increased level of depression or other psychiatric illness.

All visits to the study psychiatrist and interaction with the Unit for Internet Psychiatry are documented in health care journals according to routine and practice in the psychiatry unit at Stockholm Healthcare Region.

10.2 Laboratory Safety Assessments

Blood analyses for control of thyroid function (TSH, T3 and T4) and Haemoglobin (Hb) will be evaluated as done in clinical practice and in case of values above or below reference values in pregnant women the patients will be contacted and necessary action will be undertaken.
Other blood tests, e.g. samples for plasma concentrations of sertraline, other endocrinological tests (apart from thyroid hormones) and DNA from whole blood for analyses of genetic variants controlling metabolism and drug transport will be banked and analysed when all study samples are collected. Cell separation will be performed within 6 hours for epigenetic and telomere biology variables testing. All blood samples from the infants in the umbilical cord will be analysed later, cell separation will be done within 6 hours. The capillary blood glucose will be measured immediately and if below reference values measurements will be taken to restore normal levels.

11 PROCEEDINGS FOR ADVERSE EVENTS

11.1 Definition of Adverse Events

The drug sertraline used in this study is one of the drugs of choice according to the treatment recommendations from the Drug and Therapeutics Committee at Stockholm County Board (Läkemedelskommittén, SLL Kloka Listan: www.janusinfo.se/Beslutsstod/Kloka-Listan/Kloka-listan-2014) so the adverse effects and adverse reactions are known to the study psychiatrists.

In the study, the definitions of adverse events (AE) serious adverse events (SAE) and suspected unexpected Serious Adverse Reactions (SUSAR) relate to any study patient regardless of if this patient belongs to the group receiving sertraline and I-CBT or placebo and I-CBT. The adverse events can also be related to the I-CBT.

An adverse event (AE) is defined as an event that is any undesirable experience associated with the use of the medical product in this case sertraline or placebo.
A serious adverse event (SAE) is defined as death, a life-threatening event, hospitalization (initial or prolonged), disability, permanent damage or congenital anomaly/birth defect in the infant. **Any suspected SAE should be reported in a special form and sent within 24 hours by e-mail to the sponsor.**

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed is the applicable SPC, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Adverse events (AE) or serious adverse events (SAE) are any undesirable experience reported by the patient, reported in interviews, questionnaires, or results from laboratory tests that come to the knowledge of the investigator, regardless of the relation to the drug/placebo used for treatment in the study. The sponsor will report all SUSARs to all Principal Investigators involved in trials with the IMP.

There is an additional data monitoring and safety committee (DMC) consisting of independent senior researchers from Karolinska Institutet, Umeå University and Lund University (See section 8.3). This committee can at any time if there is any suspicion of a serious adverse event break the code and undertake necessary precautions.
It is well documented that the ICBT may cause stress as the participants sometimes feel they do not have time to fulfil the ICBT. Unexpected reactions on ICBT will also be reported according to procedures used routinely in the Department for Internet Psychiatry (IPSY) at Psychiatry Southwest, Stockholm Healthcare Region. These reports of adverse events will be reported further to the study physician, who will report to the sponsor and in due cases report to Karolinska Trial Alliance (KTA) for further reports to EduraVigilance.

The sponsor will each year of the study submit a safety report to The Swedish Medical Products Agency.

12 DATA MANAGEMENT

All data will be collected in a database. Each subject in the study will have a study number to identify the subject. The code will be kept on paper in a locked cupboard.

12.1 Statistical Analysis

The main analyses will be done according to the intention to treat principle. Data will also be analysed per protocol to achieve an efficacy analysis. The primary endpoint, results of BSID III® will be analysed with Student's T-test. Multiple imputation will be used for missing data. The variables used in the imputation mode will be smoking, ADHD, education level and parity. All patients' demographic data will be analysed by descriptive (mean, median and range) statistics. Fisher's exact test will be used for dichotomous variables such as infant sex, mother's smoking and optimal/suboptimal neurology at Hammersmith neonatal neurological examination. Throughout the analysis, the mean and standard deviation will be calculated for all continuous data using Student's T-test. The non-normally distributed continuous variables, including the results from Hammersmith neurological scales will be analysed with the Mann-Whitney U-test and the results of MADRS by Cohen's effect size. For categorical variables, absolute frequency, percentages and/or proportions are calculated and Fishers exact test will be used.

The treatment effect analysis of the add-on effect of sertraline to ICBT will be a multilevel model for longitudinal data with timepoints nested within individuals (a.k.a. Growth Curve Modelling) using MADRS-S scores from baseline, each of the 12 weeks in treatment, and post treatment. A p-value of <0.05 will be considered significant. Sub group analyses will be performed for several subgroups such as prematurity, smokers, ADHD, parity, maternal age and education level. Spearman's correlation test will be used to test the correlation between maternal and infant plasma sertraline concentration.

12.2 Determination of Sample Size

For the primary objective
The sample size is calculated to be able to detect a difference of 7 points (SD 0.5) points with a power of 80% (α: 0, 05) in the results when testing with BSID-III ® at 2 years of age. It is estimated to give a clinical significant difference. This means that the study will require a sample of 73 participating children in each

group. We assume a superiority effect when exposed to sertraline in utero (effect on BSID). If no difference between groups is detected various non-inferiority analyses will be pursued.

For the secondary objective

The additional effect of sertraline as compared to standard ICBT plus placebo will be evaluated by comparing effects on MADRS-S scores between the groups. Data on the total effect of CBT combined with antidepressant therapy is limited. The standardized effect of psychotherapy can be as high as 0.74 when compared to placebo and 0.38 when compared to face-to-face psychotherapy (35). ICBT is largely self-directed even with therapist guidance, which is likely to put a higher demand on the patients in terms of initiative and maintaining the motivation compared to face-to-face-treatment. Therefore, it is likely that the added effect of SSRI will be larger than what has been found in face-to-face CBT, though not as large as when compared to placebo alone. We therefore hypothesize a standardized effect size of *d*=0.50 (Cohen). This is also the minimal added effect that we would consider clinically relevant considering the possibility of negative side effects and the documented efficacy of ICBT alone.(34) A sample size calculation with standardized effect equal to 0.5 (Cohen), alfa-value=0.05 and power 80% requires 64 persons in each group. Therefore to recruit 100 patients in each group will fulfil the power calculation.

12.3 Analysis of risk –benefit

The main outcome of this study is to evaluate the cognitive development in the children exposed to sertraline in fetal life. Usually these studies are performed on cohorts. In the present study we have the opportunity to compare the outcome in two groups of children, whose mothers have received the same treatment except for the treatment with the active drug (sertraline). For the second endpoint, the level of maternal depression, there is a possibility to evaluate the effect of the add-on treatment with sertraline to the ICBT. Sertraline is recommended for treatment of moderate depression, and is used in clinical practices. The risk for the women or their children is not increased compared to the regular treatment today. On the contrary, the women will have a more thorough follow-up of their treatment than in clinical practice.

12.4 Control of quality and guarantee of quality

There will an independent monitor from Karolinska Trial Alliance (KTA), Karolinska University Hospital, who will continuously control that the researchers follow the study protocol. The staff at KTA has well documented knowledge and formal education in Good Clinical Practice GCP.

12.5 Insurance of patients

All patients included in the study are included in The Patient Claims Panel Insurance for patients in Sweden. (www.patientskadenamnden.se/system/in-english/).

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

If your work does not currently contain an item consider adding it. If you are certain that an item does not apply to your work, write 'n/a'. If you like, you can provide a short reason.

Upload this checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1, 3
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	14
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	14
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	1

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11, 13
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions:	#11a	Interventions for each group with sufficient detail to	7

description		allow replication, including how and when they will be administered	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5 (fig1)
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any	6

		planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5,6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8, 9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the	9

		protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial	13

		registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5, fig1
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Use of professional writers not intended
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Publication of full protocol possibly with this manuscript.

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Are attached. English translations can be published as appendices.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9