RESEARCH PROTOCOL

Father Trials: Video Feedback and Prenatal and Postnatal Parenting

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PROTOCOL TITLE '*Father Trials: Video Feedback and Prenatal and Postnatal Parenting*'

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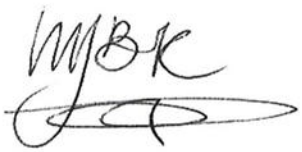
[Coordinating Investigator/Project leader/Principal Investigator]: ***<please include name and function>***	 Prof. dr. M.J. Bakermans-Kranenburg Centre for Child and Family Studies, Leiden University	08-03-2018

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
IB	**Investigator's Brochure**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
VIPP	**Video Feedback Intervention to promote Positive Parenting**
VIPP-PRE	**The Prenatal Video Feedback Intervention to promote Positive Parenting**

SUMMARY

Rationale:

We propose to conduct a randomized controlled trial (RCT) with a between-subject design in a critical phase of parenthood: the transition to having the first baby. We focus on the 50% of parents who have been neglected in parenting research and –until recently- in family policies: fathers. In most western countries fathers have increased their participation in parenting over the past decades. And even though in most families the participation of fathers in child rearing is modest, the parental role of fathers is highly relevant for child development (e.g., Kok et al., 2015; Ramchandani et al., 2005). We will test the effects of a prenatal version of the Video Feedback Intervention to promote Positive Parenting (VIPP, Juffer et al., 2008) on fathers' hormonal levels, on their processing of infant signals, and on their parenting behavior, including the quantity (involvement) and quality (sensitivity) of father-child interaction. The proposed study tests whether exposure to and interaction with the unborn infant increase the father's involvement during pregnancy and after birth. A special focus is on a dimension of parenting that has received considerable attention in animal research but, despite its evolutionary importance, not in studies on humans: the role of the parent as protector.

Objective:

In this RCT the following hypotheses will be tested:

1. The Prenatal Video Feedback Intervention to promote Positive Parenting (VIPP-PRE) results in different hormonal, neural, and behavioral responses to infant stimuli and video clips designed to elicit protective parenting
2. VIPP-PRE promotes fathers' parenting in terms of quantity (involvement) and quality (sensitive interaction)
3. VIPP-PRE affects fathers' basal hormonal levels (i.e. oxytocin, vasopressin, cortisol, estradiol, and testosterone), which in turn may mediate neural and behavioral effects.

Secondary objective

We will examine the extent to which effects of the VIPP-PRE intervention are moderated by fathers' early childhood experiences. Although fathers' early childhood experiences are known to moderate the effects of nasally administered oxytocin, it is not yet clear whether this also holds for endogenously produced oxytocin.

Study design:

The RCT includes an experimental group and a control group, and will be conducted during pregnancy (i.e. gestational age 20-30 weeks). The interventions start 1-2 weeks after the pretest. The first posttest is administered 1-2 weeks after the intervention, and a follow-up 5-6 months later (i.e. infant is 8 weeks old).

Study population:
A total of 140 (2x70) fathers having their first baby will be recruited to take part in the study.

Intervention (if applicable):
The VIPP-PRE consists of three sessions between the 21th and 30th week of pregnancy. Parents are seenby an intervener and a prenatal ultrasound professional. The visits take place every 1-2 weeks and last for approximately one hour. Fathers will be invited to interact with the fetus both verbally and by touching and softly massaging the infant through the mother's abdominal wall. The baby's behavior will be made visible through ultrasound.

Main study parameters/endpoints:
The main study parameters are:

- Parenting behavior, including physiological response to infant stimuli ("handgrip task"), sensitivity ("quality of care"), involvement ("quantity of care"), and protection. We will examine the effects of VIPP-PRE on these parenting behaviors.
- Activity in brain areas associated with parenting. We will examine the effects of VIPP-PRE on activity in these areas in fathers during the processing of infant signals and brief video vignettes designed to elicit protective parenting.
- Oxytocin, vasopressin, and estradiol levels will be assessed in saliva. Cortisol and testosterone will be assessed in both saliva and hair samples. Saliva samples are used to measure current hormonal levels. Hair samples provide information on hormone levels in past period: as human scalp hair grows approximately 1 cm per month, hormone concentrations in 1 cm hair reflect the mean exposure of 1 month.

These assessments have all previously been approved by the METC and the CCMO (see NL54702.058.15 and nr. NL49069.000.14) and tested in a pilot sample (see NL54702.058.15 and P15.359). These measures take place at the LUMC.

In line with our pilot study (see NL54702.058.15), participants will answer questions through a mobile app and online questionnaires at home. Similarly, the partners of the participants will fill out online questionnaires. Participants will provide ten additional saliva samples in between lab visits at the LUMC.

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

There are no risks associated with the assessments used in this study. No adverse effects have been reported in participants/patients undergoing MRI at the currently available field strengths. The short sound fragment used in the Auditory Startling Task is not harmful for the hearing of both father and infant. The burden associated with participation (producing ten saliva samples, three visits to the LUMC, three intervention sessions, online and app questions) has been approved by the Toetsingscommisie Ethiek Pedagogische Wetenschappen (see ECPW2017-170). The use of non-medical prenatal ultrasound in this study is strictly regulated and considered safe.

Once we understand the neurobiological underpinnings of good-enough and poor parental sensitivity and protection, better attempts can be made to improve parenting and reduce the adverse effects of poor parenting. Thus, the importance of the benefits gained from this research outweighs the minimal risks involved.

1. INTRODUCTION AND RATIONALE

We propose to conduct a randomized controlled trial (RCT) with a between-subject design in a critical phase of parenthood: the transition to having the first baby. We focus on the 50% of parents who have been neglected in parenting research and –until recently- in family policies: fathers. In most western countries fathers have increased their participation in parenting over the past decades. And even though in most families the participation of fathers in child rearing is modest, the parental role of fathers is highly relevant for child development (e.g., Kok et al., 2015; Ramchandani et al., 2005). We will test the effects of the Video Feedback Intervention to promote Positive Parenting (VIPP, Juffer et al., 2008) on fathers' hormonal levels, on their processing of infant signals, and on their parenting behavior, including the quantity (involvement) and quality (sensitivity) of father-child interaction.

A special focus is on a dimension of parenting that has received considerable attention in animal research but, despite its evolutionary importance, not in studies on humans: the role of the parent as protector. Protection is a crucial aspect of human parenting. This is perhaps demonstrated most convincingly when we are confronted with the absence of parental protection, i.e. neglect, or the opposite of parental protection, i.e. child physical abuse. Neglect has the highest prevalence of all categories of child maltreatment and has serious consequences for many domains of child development (Gilbert et al., 2009). Physical abuse has its peaks in early childhood, and infant crying is a documented trigger of early physical abuse (Barr et al., 2006).

In animals, parenting is under strong hormonal control, and it would be naive to suppose that this is very different for human parents. Hormones that have been documented or suggested to play a role in human fathers' parenting are oxytocin, vasopressin, testosterone, and cortisol (Apter-Levi et al., 2014; Atzil et al., 2012; Bick & Dozier, 2010; Feldman & Bakermans-Kranenburg, 2017).

We will test the effects of the VIPP on fathers. For over 20 years now, our Leiden group has been investing in the development and evaluation of the VIPP intervention program, which aims to enhance parental sensitivity by, e.g., increasing parental awareness of subtle infant signals, speaking for the baby, and highlighting chains of sensitive behavior. The VIPP intervention program has been thoroughly evaluated in RCTs, showing its effectiveness on parental sensitivity and infant attachment, but so far only with mothers and (female) professional caregivers. Furthermore, existing RCTs of VIPP have overlooked pregnancy as an important window of opportunity.

Here, we propose to conduct the first RCT of VIPP-PRE, in a study during pregnancy (i.e. gestational age 20-30 weeks) and with a focus on fathers. Intervention programs such as the VIPP may exert their effects over longer periods of time and can thus be adequately tested with between-subject designs that include follow-up assessments, as is proposed here. The first posttest is administered one week after the intervention, and a follow-up 5 to 6 months later (i.e. +2 months). In the Prenatal Video Feedback Intervention to promote Positive Parenting (VIPP-PRE), we aim to promote an early relationship between father and child using intra-uterine video-clips. Attending prenatal ultrasounds have been found to emphasize the reality of the pregnancy and child, and promote the development of prenatal paternal attachment (Walsh et al., 2014). Also, fetuses have been shown to react to touch (Marx and Nagy, 2015;) and both maternal (Ferrari et al., 2016; Voegtline et al., 2013) and paternal voices (Lee and Kisilevsky, 2013). Therefore, we use intra-uterine video-clips to guide the expectant fathers in interacting with their unborn child.

No RCT data for VIPP with fathers exist, and that is an important reason for this study. Fortunately, there is observational research suggesting that VIPP with fathers is feasible (Lawrence et al., 2012). Specifically, it is argued that the VIPP intervention has a number of key features that make it suitable for use with fathers (as well as mothers). First and foremost, it is a brief intervention. Both features are likely to enhance the engagement and participation of fathers. Second, it focuses principally on positive aspects of parent-child interaction; building on the strengths of the parent. Third, the focus is directly on parent-infant interaction through the use of video, so it holds up ‘a mirror of their own daily interactions with their child’, rather than relying on videos of other parent-infant pairs to demonstrate parenting strategies. Moreover, delivery of the VIPP can be adapted to the fathers’ wishes with respect to the timing of sessions. This flexibility, is fundamental to successful outcomes and will be accomplished in our study.

The aim of the proposed VIPP intervention is both practical and theoretical: Testing the efficacy of the behavioral experimental interventions in boosting fathers’ participation in caregiving activities has clear practical significance (for fathers, mothers, children, and society), while examining the mechanisms is crucial for the development of theory on the interplay between neuroscience and behavior. Hormonal changes during pregnancy prepare future mothers for their new role as parents. In fathers such changes may be triggered by prenatal interventions (just as in male virgin rats exposure to pups increases caregiving behavior, Numan, 2014), such as intended in the VIPP-PRE study.

1.1. ‘Fathering’: Care, Protection, and Response to infant crying

1.1.a Care

Father care comes in different quantities and different qualities. In most western countries fathers have increased their participation in parenting over the past decades, but maternal involvement remains substantially higher. Fathers spend on average less than half as much time in direct one-on-one interaction with their children as mothers (Huerta et al., 2013), especially in early childhood (Wood & Repetti, 2004). Although the quantity of time invested in parenting is generally considered less important than quality ("quality time"), it is easy to see that it takes considerable time to get to know an infant, become aware of its preferences, and read its signals (Bowlby, 1989). For most young fathers, spending more time on interaction with their infant will add to the quality of the interaction.

In research on parenting *quality*, parental sensitivity is a key construct. It refers to the ability to attend to infant signals and to respond promptly and appropriately (Ainsworth et al., 1974). Similarly to the pattern of associations for mothers, higher levels of paternal sensitivity predict more favorable child outcomes (Lewis & Lamb, 2003). Sensitive parenting starts with the processing of infant signals, which has shown to be affected by oxytocin levels (Riem et al., 2011), but may also be affected by vasopressin levels. These hormones may play a role in fathers' processing of infant signals as well, but the direction of the association is as yet unclear.

Once infant signals have been processed, the caregiving response may be more or less sensitive. Sensitive responsiveness has been operationalized in various ways, including dimensions such as emotional support, stimulation, and mutuality. Conspicuously absent among these dimensions is that of parental protection. It is exactly this protective aspect of the caregiving system that has largely been neglected in studies of human parenting. In a comprehensive review on parental 'precaution', the lack of studies employing various cues of potential threat to offspring was noted as a significant limitation (Hahn-Holbrook, Holbrook, & Haselton, 2011). The proposed study intends to chart this unexplored territory.

Fathers and mothers are both responsible for the protection of offspring, but the scant existing research into parental protection in response to cues of potential danger has involved mothers (Hahn-Holbrook et al., 2011). However, fathers play a critical role in the protection of offspring, as is evident from the twofold increase in the likelihood of child death in traditional societies when the father is absent due to death or divorce (Hurtado & Hill, 1992). These numbers may be mitigated in modern society, but they underscore the probability that fathers have an innate tendency to protect their infants.

1.1.b Response to infant crying

With young infants, responsiveness to infant crying is central to sensitive parenting. In a randomized controlled trial with intranasally administered oxytocin we found that in females

without children of their own oxytocin administration reduced activation in the amygdala (related to anxiety and aversion) and increased activation in the insula and inferior frontal gyrus (involved in empathy) (Riem et al., 2011). On a behavioral level, participants used less excessive force with a hand-grip dynamometer when listening to infant cry sounds after intranasal oxytocin (Bakermans-Kranenburg et al., 2012).

1.2. Endocrine processes of fathering

An important question is how sensitivity and protective parenting are associated with hormone levels, in particular oxytocin and vasopressin. A number of neuropeptides and hormones (including, e.g., prolactin and progesterone) are involved in 'fathering', in the sense of 'being a father' (Rilling & Young, 2014). Four hormones are of particular relevance: oxytocin, vasopressin, cortisol, and testosterone. In the proposed studies, these four hormonal levels will be measured. We have demonstrated increased sensitivity after intranasal oxytocin administration in fathers, both with normally developing children and with children with autism (Naber et al., 2010). Examining oxytocin in mothers and fathers interacting with their 4-6 month old infants, Feldman and colleagues found that higher maternal oxytocin levels were associated with more affectionate touch, and higher paternal oxytocin levels were associated with more stimulatory play (Feldman et al., 2010). Less is known about vasopressin. While both oxytocin and vasopressin have been associated with social and affiliative behavior, in males vasopressin may be of particular importance (Taylor, Saphire-Bernstein, & Seeman, 2010). In expectant fathers, vasopressin administration increased fathers' implicit caregiving interests (Cohen-Bendahan et al., 2015). Moreover, vasopressin has been associated with increased stimulatory contact between fathers and their 4- to 6-month-old infants (Apter-Levi et al., 2014). While testosterone has been associated with aggressive behavior in general, vasopressin has been suggested to be associated specifically with protective aggressive behavior (Van Anders et al., 2011). Fathers with lower basal testosterone levels show more optimal parenting behavior (Weisman, Zagoory-Sharon, & Feldman, 2014) and feel more sympathy when listening to infant cries (Fleming, Corter, Stallings, & Steiner, 2002). At the same time, exposure to cry stimuli can increase fathers' testosterone levels (Fleming et al., 2002). Besides basal testosterone levels, diurnal variability in testosterone levels have been associated with parental sensitivity and respect for children's autonomy (Endendijk et al., 2016). Testosterone may exert its effects directly or indirectly: In the central nervous system, testosterone is metabolized to estradiol, which in turn is critical for the synthesis of oxytocin (Choleris, Devidze, Kavaliers, & Pfaff, 2008). Moreover, testosterone facilitates vasopressin production (de Vries, 2008). Cortisol is involved in the regulation of parenting behaviors in mothers and fathers (Fleming et al., 1997; Wynne-Edwards, 2001). While the expression of

maternal behavior in the newborn period has been associated with higher cortisol levels (Fleming, Steiner & Anderson, 1987), most studies point to associations between higher cortisol and less optimal parenting, expressed as higher intrusiveness, lower sensitivity, and greater tension (Feldman, Singer, & Zagoory, 2010).

1.3. Neurobiological processing

Mapping parental brain responses to infant stimuli using fMRI has increased our knowledge of brain processes involved in parenting sensitivity. Brain regions expected to be important to parenting are circuitries related to (1) arousal/salience (amygdala, ventral striatum), (2) reflexive care (hypothalamus), (3) emotion regulation (insula, medial prefrontal cortex, anterior cingulate cortex), and cognitive / empathic processing (insula, inferior frontal and orbitofrontal gyri, temporoparietal junction) (Parsons et al., 2010; Swain et al., 2014). Exposing parents to child stimuli in fMRI studies activates neural systems involved in these regions. Rilling suggests that there may be an optimal range of activation that supports appropriate parenting (Rilling, 2013). Under-activation of the amygdala and insula may lead to insufficient response (neglect), whereas over-activation could lead to over-arousal, which would interfere with sensitive caregiving. For protective parenting responses, the amygdala may play a central role. The amygdala functions as an “alarm” to relay signals of threat. Infants are rewarding attachment-objects, motivating parental care and attention, which intensifies protection of the child against potential threats (Szechtman & Woody, 2004).

The infant stimuli to be used in this study are related to stress or distress. Infant smiles and laughter are also important stimuli, and we have used them before (Riem et al., 2012), but sensitivity to distress signals has been shown to be a better predictor of child outcomes than sensitivity to non-distress cues (Leerkes, Nayena Blankson, & O'Brien, 2009; McElwain & Booth-Laforce, 2006). Moreover, many imaging studies suffer from a brain-behavior gap (no associations between brain activity and observed behavior), but amygdala and frontal cortex activity in response to infant crying has been found to be related to observed maternal sensitivity (Kim et al., 2011).

2. OBJECTIVES

Primary Objective:
In a randomized control trial (RCT) the following hypotheses will be tested:

1. VIPP-PRE results in different hormonal, neural, and behavioral responses to infant stimuli and video clips designed to elicit protective parenting
2. VIPP-PRE promotes fathers' parenting in terms of quantity (involvement) and quality (sensitive interaction)
3. VIPP-PRE affects fathers' basal hormonal levels (i.e. oxytocin, vasopressin, cortisol, estradiol, and testosterone), which in turn may mediate neural and behavioral effects.

Secondary Objective(s):
We will examine the extent to which effects of the VIPP-PRE intervention are moderated by fathers' early childhood experiences. Although fathers' early childhood experiences are known to moderate the effects of nasally administered oxytocin, it is not yet clear whether this also holds for endogenously produced oxytocin.

3. STUDY DESIGN

We propose to conduct the first RCT of VIPP with fathers during pregnancy. The RCT includes an experimental group that will receive the VIPP-PRE intervention, and a control group with a dummy intervention. Expectant fathers will participate in a pretest around the 20th week of pregnancy. The VIPP-PRE intervention consists of three sessions between the 21st and 30th week of pregnancy. The first posttest is administered one week after the intervention, and a follow-up four months later. The pretest, posttest, and follow-up sessions take place in the MRI facilities in the LUMC.

4. STUDY POPULATION

4.1 Population (base)

A total of 140 (2x70) fathers having their first baby will be recruited to take part in the study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Fathers having their first baby.
- The parents must have had the 20-week medical ultrasound via regular health care services.
- Partners of the fathers must be low-risk expecting women with uncomplicated singleton pregnancies between the 21th and 30th week of gestation.

4.3 Exclusion criteria

- Not living in the same house as their partner
- Not fluent in Dutch
- Endocrine disorders
- Alcohol and drug abuse
- Use of medication potentially interfering with the endocrine system
- MRI contraindications, including metallic foreign objects, neurological disorder and claustrophobia
- Psychiatric disorder
- Cardiovascular disease
- Birth defects in the families of either the father or the mother.
- Further, fathers with partners who meet any of the following criteria will be excluded: alcohol, tobacco or illicit drug use during pregnancy, BMI over 30 before pregnancy, or abnormalities found during the regular 20-week ultrasound.

Parents who absolutely do not want to know the gender of their unborn baby are advised to carefully consider participation, since this might unintentionally be visible during ultrasound.

4.4 Sample size calculation

The sample size will be 140 (N = 70 in each of the conditions), with 15% oversampling to compensate for attrition. On the basis of an expected meta-analytic effect size of r = .24 for the VIPP interventions (Juffer et al, 2010, 2017), power is ≥ .82 (G*Power 3.1.9). This sample size provides also sufficient power to test indirect effects through hormone levels and neural processing, as the power of the test of indirect effects is (substantially) greater than the power of the test of direct effects (Kenny & Judd, 2014).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The experimental group (half of the sample, randomly selected) will receive an intervention, the Video-feedback Intervention to promote Positive Parenting – Prenatal (VIPP-PRE; Juffer et al., 2008). This intervention focuses on enhancing parenting sensitivity. Studies using the VIPP intervention have repeatedly been approved by the CCMO (document nr: NL49069.000.14 and NL50277.058.14). The VIPP is the only parenting intervention which is indicated as established effective in the Database of Effective Youth Intervention from the Netherlands Youth Institute (see www.nji.nl). VIPP studies have almost all focused exclusively on mothers and have paid little attention to the role of fathers. One notable exception is the study of Lawrence et al. (2012), showing that the VIPP is suitable for use with fathers and that no specific changes to the intervention are needed. For the current study the VIPP method has been adapted for prenatal use, with ultrasound instead of regular video fragments.

Content of the intervention

The VIPP-PRE consists of three sessions between the 21st and 30th week of pregnancy. Each session lasts for approximately one hour and the sessions take place every 1-2 weeks. Fathers will be invited to interact with the fetus both verbally and by touching and softly massaging the infant through the mother's abdominal wall. For a more detailed description of the intervention see Document F21. This description has previously been approved by the Toetsingscommisie Ethiek Pedagogische Wetenschappen under project number ECPW2017-170. Fathers will be asked to 'communicate' with their unborn babies, made visible through ultrasound. Their partners are thus asked to cooperate and have the ultrasound made. During each session, the first minutes of the ultrasound will be shared with both parents, taking into account the mothers' wish to see her baby as well. The baby's behavior will be made visible through ultrasound.

Control condition

Fathers in the control group will receive telephone calls from a research assistant during the same period and with the same frequency (dummy intervention). During these telephone calls, fathers will be asked about the development of the pregnancy.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. NON-INVESTIGATIONAL PRODUCT

<For products to be used as in usual clinical practice the information can be limited to the chapters 7.1, 7.6 and 7.7 >

6.1 Name and description of non-investigational product(s)

Phillips Lumify, a portable ultrasound system.

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

Ultrasound images of the unborn child of father's in the intervention group will be obtained during sessions with a prenatal ultrasound professional. In accordance with the ALARA principle (As Low As Reasonably Achievable, e.g. AIUM, 2014), scanning time as well as thermal output will be minimized. Specifically, we will use the ultrasound for a maximum of 10 minutes, for a total of 3 times with a one week interval. This is clearly within the range of recommended scanning times, see BMUS, 2010; Harris et al., 2016).

6.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main study parameters are:

- Parenting behavior, including physiological response to infant stimuli ("handgrip task"), sensitivity ("quality of care"), involvement ("quantity of care"), and protection. We will examine the effects of VIPP-PRE on these parenting behaviors.
- Activity in brain areas associated with parenting. We will examine the effects of VIPP-PRE on activity in these areas in fathers during the processing of infant signals and brief video vignettes designed to elicit protective parenting.
- Oxytocin, vasopressin, and estradiol levels will be assessed in saliva. Cortisol and testosterone will be assessed in both saliva and hair samples. Saliva samples are used to measure current hormonal levels. Hair samples provide information on hormone levels in past period: as human scalp hair grows approximately 1 cm per month, hormone concentrations in 1 cm hair reflect the mean exposure of 1 month.

7.1.2 Secondary study parameters/endpoints (if applicable)

We will examine the extent to which effects of VIPP intervention are moderated by fathers' early childhood experiences.

7.1.3 Other study parameters (if applicable)

Measures of sports, food and drinks, and medication use at assessment days (pretest, posttest, follow-up) and the day before, health status, pregnancy/child related events and general wellbeing during the week leading up to assessment days, quality of sleep during month prior to assessment days, prenatal preparation and number of prenatal ultrasounds up to each assessment day, due date / child's date of birth and current mood during each lab visit. Other father variables: child care experience, child feeding experience, hours per week spent with infant, day care arrangements, moral identity, prenatal/postnatal parental protection, and sensory-processing sensitivity, retrospective perceptions of exposure to parental behavior, child discipline and maltreatment. For both fathers and mothers: date of birth, education, family income, task division, family functioning, daily life, perinatal depression, parenting attitude and behavior, gender specific orientation, and course

of pregnancy. Mother variables: report of partners' prenatal/postnatal parental protection, smoking and drinking during and after pregnancy, course of pregnancy and birth, and child's health.

7.2 Randomisation, blinding and treatment allocation

Participants will be assigned randomly to either the intervention or the control condition, with no expected group differences. As listed above, the intervention group will receive the VIPP-PRE intervention between the 21st and 30th week of pregnancy whereas the control group will receive telephone calls.

7.3 Study procedures

The pretest, post-test and follow-up assessments have all previously been approved by the METC and the CCMO (see document nr: NL54702.058.15) and tested in a pilot sample (see NL54702.058.15). They include the following assessments (1) hormonal (assessment of oxytocin, vasopressin, and estradiol levels in salvia and assessment of testosterone and cortisol levels in both saliva and hair samples; see document nr. NL49069.000.14), (2) neural (fMRI: processing infants stimuli and video clips designed to elicit protective parenting), and (3) behavioral (handgrip during infant stimuli, quantity of care, quality of care, and protection) measures. These measures take place at the LUMC. In line with our pilot study (see NL54702.058.15), participants will answer questions through a mobile app and online questionnaires at home. Similarly, the partners of the participants will fill out online questionnaires. Participants will provide additional saliva samples in between lab visits at the LUMC. In the week after the follow-up, a home visit will be made for the observation of paternal sensitivity with his own baby, at which time another 2 saliva samples will be collected. See figure S1 for more information.

The assessments in each session, as presented in Figure S1:

1. Introduction, questionnaires
2. Saliva and hair collection (for assessment of oxytocin, vasopressin, testosterone, estradiol and cortisol levels). Saliva samples will be taken before the start of the free play session (baseline), and after the free play session. Hair samples will be taken upon arrival and contain around 100 hairs from the posterior vertex of the scalp.
3. Neural assessments: (f)MRI (60 minutes). Brain activity will be recorded during processing infant stimuli and video vignettes designed to elicit protective parenting.

   Processing infant signals
   Exposure to infant sounds and scrambled control stimuli that are identical to the original auditory stimuli in terms of duration, intensity, spectral content, and amplitude envelope, but lacking recognizable qualities. Participants report on the perceived urgency of the sounds, and on their perception of the child's state (i.e. annoyed, sad).

   Protective parenting
   Video vignettes designed to elicit protective parenting preceded by pictures of the participants' own or an unfamiliar child. Brief video vignettes display non-threatening situations (e.g. a baby in a maxicosi next to a car on a parking lot), and threatening situations (e.g. a baby in a maxicosi on a parking lot within reach of a parking car). The videos have been recorded using a lifelike doll. In order to optimize identification by the participant, faces of both the doll and the actors are not visible. In a pilot study, threatening videos were rated as significantly more threatening and arousing than control videos.

4. Behavioral assessments: (1) Handgrip during infant stimuli, (2) Quantity of care, (3) Quality of care, and (4) Protection.

   Handgrip during infant stimuli
   Participants are asked to squeeze a handgrip dynamometer at full and half strength, thus setting their own baseline, and then at 50% of their maximal handgrip strength. They perform as many trials as necessary in order to be able to squeeze at half strength, with their performance displayed on a

monitor. Participants are then requested to squeeze the handgrip dynamometer at full and half strength without receiving feedback, while listening to infant stimuli and while listening to a scrambled sound acoustically similar to the cry. With the sounds, the picture of an infant face will be shown. The picture will display the father's own baby or an unfamiliar baby. We have extended experience with this measure (Bakermans-Kranenburg et al., 2012; Compier-de Block et al., 2015).

Quantity of Care (involvement)
Father involvement in daily caregiving activities will be assessed with self-report, partner report, and e-diaries, using mobile technology in order to have real-time assessments. Fathers are asked to download an app on their mobile phone and receive brief questions about their activities, to be answered throughout the day.

Quality of care (sensitivity)
The quality of care (sensitivity) will be observed during parent-child interaction (free play). Secondly, the Five Minute Speech Sample (FMSS) will be used to assess fathers' Expressed Emotions as an index for a sensitive parenting attitude. In the FMSS, parents are asked to describe their child and their relationship with their child. Thirdly, sensitivity will be observed during when fathers are asked to take care of a life-like doll for 10-min (Leiden Infant Simulator Sensitivity Assessment (LISSA); see Bakermans-Kranenburg et al., 2015). Moreover, a brief observation of father-infant interaction (father with his own infant) will be made.

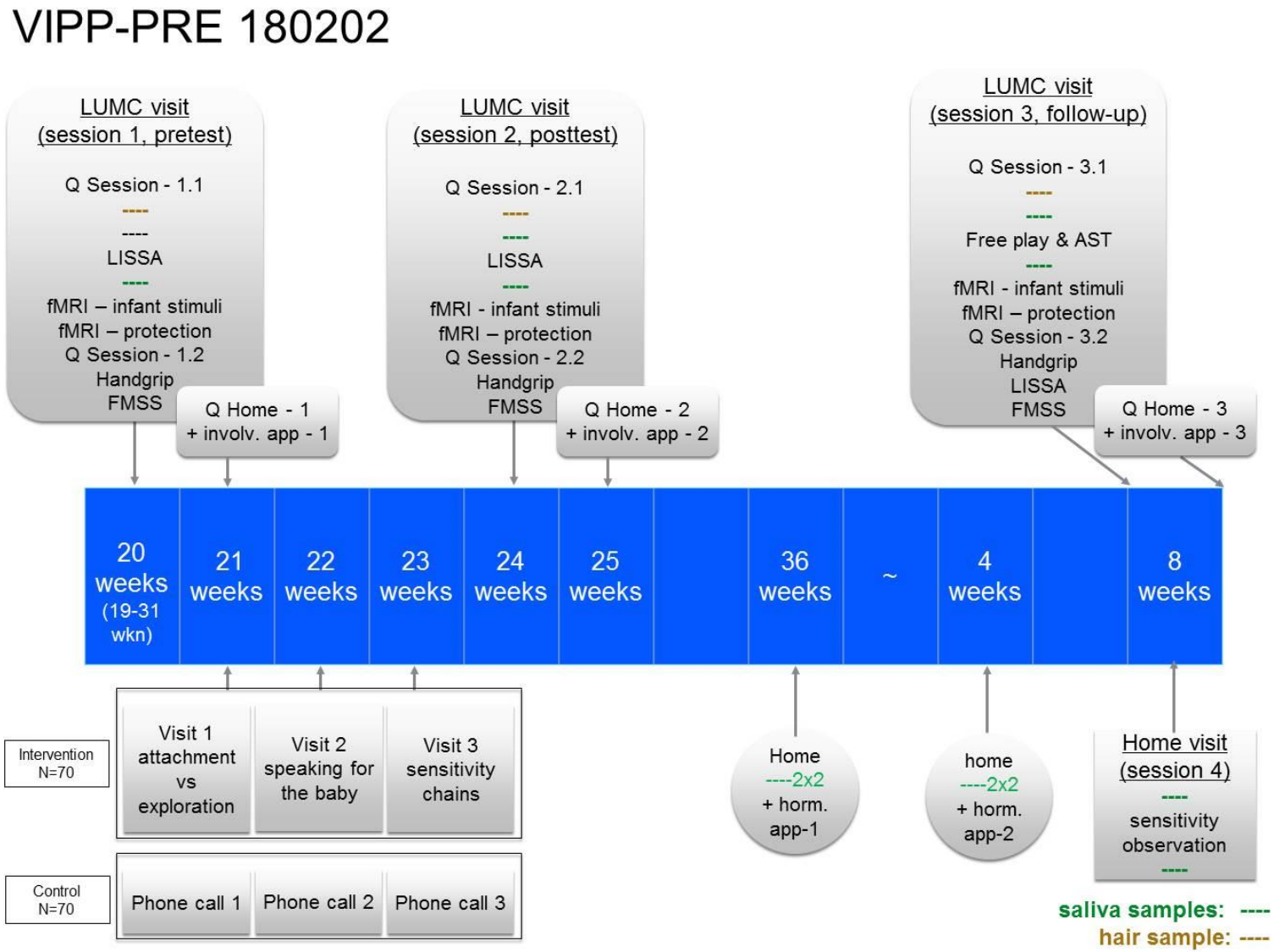
Protection (only during follow-up session)
The Auditory Startling Task (AST) will be used to observe parental protective behavior. The procedure has been used in other labs as well (Herzliya university Tel Aviv, with prof. Dana Shai) with infants and their parents. While the participant plays with the baby, a short sound fragment will be heard. The sound consists of white noise (80-db) and is programmed for 10 seconds with short breaks. This sound is loud enough to elicit a response from the baby, without harming the infant's hearing. At the end of the sound fragment, the research assistant enters the room and apologizes for the sound: "I am so sorry; we had some technical problems and took me a moment to get things under control. Sorry. So, let's move on…". The participant is debriefed about

the purpose of the sound fragment at the end of the session. Secondly, protection will be assessed with partner report, using a questionnaire on the extent to which fathers are avoiding and discouraging risk behavior (e.g. hygiene, protection of child from sickness and accidents in the prenatal and postnatal period).

Partners will be asked to accompany the fathers to the LUMC for the follow up session to provide care for the infant when the father is undergoing neural assessments. In the unlikely event the partner is not able to accompany the father and infant, we will arrange for child care by an experienced baby sitter approved by the parent.

To investigate diurnal variation of the hormones at interest, saliva will be collected at home. At two consecutive days at 36 weeks pregnancy as well as at 4 weeks post-delivery, participants will be asked to provide saliva samples twice (once in the morning, once in the evening). Reminders for sample collection will be send by telephone (app) accompanied by a short questionnaire to provide information for data quality (food, tooth brushing, activities or stress in past 30 minutes).

Figure S1: Overview and timing of assessments VIPP-PRE



7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

7.5 Replacement of individual subjects after withdrawal

If participants drop out of the study before completing the pre-test, they will be replaced by participants fulfilling the inclusion criteria.

7.6 Follow-up of subjects withdrawn from treatment

Not applicable

7.7 Premature termination of the study

< *Please describe the criteria for terminating the study prematurely and the procedures in case the study will be terminated prematurely.*>
Not applicable

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

8.3 Annual safety report

Not applicable

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

Hormonal

Effects of the VIPP-PRE intervention on hormonal responses to infant stimuli will be assessed using a General Linear Model (GLM) examining the between-group differences in within-subject (pre- and posttest) effects. Moreover, we will assess whether effects of VIPP-PRE on behavioral and neural outcomes are mediated by changes in basal hormonal levels.

Brain activity (fMRI)

Following preprocessing, both cluster corrected whole-brain, and region of interest analyses will be performed on a priori specified regions (see section 1.3), and psychophysiological-interaction (PPI) analysis will be used to examine functional connectivity among brain regions (e.g. amygdala – medial prefrontal cortex).

For the “processing infant signals” paradigms, contrasts comparing responses to infants’ sounds and scrambled control sounds will be calculated and submitted to a GLM examining the between-group differences in within-subject (pre- and posttests) effects. Moreover, by examining sound x perception interaction analyses, we will assess whether the participants’ perception of the cry sounds moderate their processing.

For the “processing threat to infant” video vignettes task, contrasts comparing responses to neutral and threatening videos, contrasts comparing child familiarity (own baby, unfamiliar baby) and their interactions will be calculated and submitted to a GLM examining the between-group (experimental and control group) differences in within-subject (pre- and posttests) effects.

Behavioral

For the “handgrip during infancy stimuli” task, handgrip dynamometer force will be submitted to GLM with a 3 (time) x 2 (sound nature: infant stimuli versus scrambled sound) x 2 (child familiarity: own baby, unfamiliar baby) design. Group (experimental or control) will be modelled as a between subject factor.

Effects of the VIPP-PRE intervention on quantity of care (self-report, partner-report and e-diaries) will be analyzed using a GLM examining the between-group (experimental and control group) differences in within-subject (pre- and posttests) effects.

For the “quality of care” task and partner-report on quality of care, a GLM will be applied to assess the between-group (experimental and control group) differences in within-subject (pre- and posttests) effects.

For the “protection” task and protection questionnaire, a GLM examining the between-group differences in within-subject (pre- and posttest) effects.

If applicable, *p*-values will be corrected for multiple comparisons using a Bonferroni correction.

9.2 Secondary study parameter(s)

To investigate potential moderation by fathers’ early life experiences, additional analyses will be conducted, including the interaction between intervention condition and fathers’ early life experiences.

9.3 Other study parameters

Analyses will be adjusted for pertinent covariates (e.g., sports, food and drinks at assessment days and the day before: see 7.1.3)

9.4 Interim analysis (if applicable)

Not applicable

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Tokyo, 2004) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The protocol of this study will be submitted to the "Commissie Medische Ethiek" (CME), Leiden Universitair Medisch Centrum, and the study will not commence before formal approval has been granted.

10.2 Recruitment and consent

A total of 140 fathers (2 x 70) will be recruited to take part in the study, with 15% oversampling to compensate for attrition. All recruitment and consent procedures listed below have recently been approved by the CCMO (document nr NL54702.058.15). Similarly to our pilot study (see NL54702.058.15), we will recruit through midwife agencies with the use of a recruitment letter (Document E3.1). Also, participants will be recruited using social media (e.g. Facebook), websites (e.g. the Leiden University website), and flyers (e.g. at pregnancy fairs, see Document E3.2), as was done in the pilot study (see NL54702.058.15). Eligible families will receive an invitation to participate in the study (Document E1.1). This invitation includes information about the study and a response card to express their interest for participation.
Interested fathers will receive a letter with detailed information about the study (Document E1.3) and will be informed that they will receive a phone call in a week. During this phone call, a research assistant will check the inclusion and exclusion criteria and answer questions. All interested fathers who reach us through other means (e.g. social media) will be sent an email with more information about the study (Document E1.2). Information collected from fathers who are excluded due to the outcome of the 20-week ultrasound will be deleted.

During all visits and sessions the fathers have the opportunity to ask questions before the intervention or measurement starts. Questions arising during the intervention or the lab visits will be answered as adequately as possible.
Written informed consent (IC) for participation, including fMRI measures, collection of saliva and hair, and the use of video/audio recordings collected during assessments (i.e. LISSA, sensitivity with own infant, and FMSS), will be obtained from the participant during the first lab visit (see Document E2.1 for the fathers' IC form). Both parents provide consent for participation of the infant, including the use of video recordings collected during assessments as well as the ultrasound images (see Document E2.1, and

Document E2.2 for the partners' IC form). The consent forms will be stored in a locked filing cabinet accessible only to the investigators. At the time of consent, any remaining questions will be answered.

In order to obtain permission for using the video material made in this study (i.e. LISSA, free play with infant, and VIPP-PRE / ultrasound images) for education and training purposes, both fathers and their partners will receive an additional consent form (Document E2.3).

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

10.4 Benefits and risks assessment, group relatedness

There are no risks associated with the assessments used in this study.

Auditory Startling Task

The short sound fragment used in the Auditory Startling Task is not harmful for the hearing of both father and infant.

MRI

No adverse effects have been reported in participants/patients undergoing MRI at the currently available field strengths. Participants will be protected against any procedural risks via a thorough pre-screening process. Structural MRI scans will be inspected by a radiologist, and in case of visible abnormalities the participant, participant's physician, and researcher will be notified. Participants' data will be handled strictly confidentially, except as required by law.

VIPP

This study concerns a behavioural intervention and not a medical trial. Several RCT's have shown the effectiveness of the VIPP intervention in improving parental sensitivity and have shown that VIPP interventions have no harmful effects (see Juffer et al., 2008). Both fathers (Lawrence, Davies and Ramchandani, 2012) and mothers (Stolk et al., 2008) have responded positively to the intervention. Parents report positive changes in parent-child interactions, parental wellbeing, and relationship quality when they were both present during the intervention (Iles et al., 2017).

Prenatal ultrasound

Ultrasound devices are unrelated to adverse maternal, perinatal or childhood outcomes (e.g. impaired physical or neurological development; see Hershkovitz et al., 2002; Torloni et al., 2009), and are considered to be safe. Scanning time in this study remains within the range of recommended scanning times (see BMUS, 2010; Harris et al., 2016; see also section 6).

Although there is no direct benefit to the participants from the proposed research, there are greater benefits to society from the potential knowledge gained from this study. Once we understand the neurobiological underpinnings of good-enough and poor parental sensitivity and protection, better attempts can be made to improve parenting and reduce the adverse effects of poor parenting. The proposed study is ground-breaking in that it includes paternal protection, an important dimension of parenting that has been neglected in all imaging studies and virtually all behavioral studies of parenting to date, maybe because of the almost exclusive focus on mothers. Furthermore, real-time measures using apps and mobile phones have been underused in research and may provide data with high ecological validity, that may differ considerably from data collected retrospectively using traditional questionnaires on time spending. Thus, the importance of the benefits gained from this research outweighs the minimal risks involved.

The privacy of individuals who participate in scientific research is protected in the Dutch Data Protection Act. The VSNU Association of Universities in the Netherlands has written a code of conduct for the use of personal data based on this law. Data will be handled strictly confidentially. Data will be stored in a confidential manner, both through the use of a numbering system and through the security of the files and computer systems. Only the researchers and research assistants have access to the data. According to the Dutch Data Protection Act, Dutch organizations can appoint a data protection officer (art. 62), but are not legally required to do so. Leiden University has chosen for a personal data contact person, who in addition to the Ethics Review Board reviews the data collection procedures. Moreover, Leiden University has a “Leiden Research data office” (http://www.library.leiden.edu/teaching-researching-publishing/publish-deposit-research/data-management/leiden-research-data-office.html) with expertise to inform and advise us in all phases.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

Participants will receive a financial reward for each lab visit completed; €25 after the first lab visit, €35 after the second lab visit, and €40 after the third lab visit. Moreover, at the final visit, participants will receive a small age-appropriate gift for the child. Participants will receive an extra €10 after the final visit if they complete at least 80% of the questions (app questions and online questionnaires). If applicable, travel allowance will be provided for participants and their partners. After completion of the study, participants in the intervention group will also receive the ultrasound images made during the VIPP-PRE.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The privacy of individuals who participate in scientific research is protected in the Dutch Data Protection Act. The VSNU Association of Universities in the Netherlands has written a code of conduct for the use of personal data based on this law. Data will be handled strictly confidentially. Data will be stored in a confidential manner, both through the use of a numbering system and through the security of the files and computer systems. Only the researchers and research assistants have access to the data. According to the Dutch Data Protection Act, Dutch organizations can appoint a data protection officer (art. 62), but are not legally required to do so. Leiden University has chosen for a personal data contact person, who in addition to the Ethics Review Board reviews the data collection procedures. Moreover, Leiden University has a “Leiden Research data office” (http://www.library.leiden.edu/teaching-researching-publishing/publish-deposit-research/data-management/leiden-research-data-office.html) with expertise to inform and advise us in all phases.

Thus, all data will be treated confidentially by using a subject number. Representations of fMRI data in publications always consist of group averages, in which individual subjects’ data cannot be recognized.

11.2 Monitoring and Quality Assurance

The proposed studies will be supported by a support group with imaging experts from both neighboring groups and abroad (Prof. Eveline Crone, Prof. Serge Rombouts, and Prof. James Rilling, Emory Univerisity, USA) and experts on hormonal assessments (Dr. Karen Grewen, University of North Carolina, Chapel Hill, USA), endocrinology (Prof. Roger Smith, University of Newcastle, Australia), and paternal behavior (Prof. Paul Ramchandani).

11.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit (home visit, one week after follow-up lab visit).

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The research questions and the design have been extensively evaluated by the European Research Council. Six very positive reviews were received. The randomized experimental study on the intriguing topic of postnatal fathering that is proposed here gives a sound basis for publications independent of the outcomes. Publication of research findings is independent of the grant supplier, whatever the outcomes are. Scientific autonomy is guaranteed (see the European Research Council guidelines).

We will disseminate findings through peer-reviewed publications. Findings will also be disseminated at leading scientific conferences, interviews, and public lectures. Participants will be informed about the study findings via newsletters.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

*< For registered products to be used within the indication and **not** in combination with other products chapter 13.1 can be skipped; explain in chapter 13.2 why 13.1 is skipped >*

a. Level of knowledge about mechanism of action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

d. Selectivity of the mechanism to target tissue in animals and/or human beings

e. Analysis of potential effect

f. Pharmacokinetic considerations

g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

12.2 Synthesis

The medical product used in this study (i.e. portable ultrasound system) will be used within the indication of the product and not in combination with other products. Therefore, chapter 12.1 is skipped.

Ultrasound devices are unrelated to adverse maternal, perinatal or childhood outcomes (e.g. impaired physical or neurological development; see Hershkovitz et al., 2002; Torloni et al., 2009), and are considered to be safe. Regardless, scanning time should always be reduced to a minimum (see also section 6). In accordance with international guidelines, scanning time in this study is limited to a maximum of 3x10 min per session, with a week interval between sessions.

Participants and their partners are informed about the use of prenatal ultrasound in the intervention group and are asked to sign a consent form which includes information about the possibility of incidental findings concerning the child's health. The probability of incidental findings are minimalized by including only healthy participants with partners experiencing uncomplicated pregnancies. Participants can only partake in the study if no abnormalities were found during the regular 20-week ultrasound. Also, participants are informed that the administered ultrasounds are not medical in nature. Therefore, abnormalities cannot be confirmed nor ruled out. For any issues concerning the health of the unborn child that arise during the making of ultrasound images, a protocol has been developed (Document F21). Also, a prenatal ultrasound professional will administer all ultrasounds used in this study. The professional will therefore be present during the intervention and can answer any possible questions about the ultrasound images. The participant's midwife will receive a letter informing them of the father's participation in the study. During each session, the first minutes of the ultrasound will be shared with both parents, taking into account the mothers' wish to see the baby as well. At this time, the current position of the child as well as the heart beating will be made visible. Without addressing this explicitly, the intervention will only take place if movement of the baby or a heartbeat can be found. A protocol has been developed for when any issues arise for when neither is found (Document F21).

The use of ultrasound in this study is necessary in order to create video material of the expectant father's interaction with his unborn child. Reviewing and discussing this material is central to the VIPP intervention. Although mothers frequently feel their unborn child during pregnancy, this is less so the case for fathers. The ultrasound images are essential for 1) seeing the 'behavior' of the child (e.g. the child is resting versus active), 2) encouraging fathers to respond appropriately (e.g. adapting the volume of his voice), and 3) being able to discuss VIPP theme's such as sensitivity during video-feedback. Taking the above mentioned regulations into account, the use of prenatal ultrasound in this study is safe.

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