

Onderzoeksc consortium voor Verloskunde, Voortplantingsgeneeskunde en Gynaecologie

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Introductie

2010 was voor de onderzoeksconsortia voor Verloskunde, Voortplantingsgeneeskunde en Gynaecologie het jaar van de toenemende samenwerking. Meer samenwerking tussen de verschillende subdisciplines, meer samenwerking tussen verschillende lijnen en meer internationale samenwerking. Broodnodige samenwerking ook, want de maatschappelijke beroering over de perinatale sterfte in ons land noopt tot breed gedragen initiatieven om de uitkomsten van zwangerschap en geboorte te verbeteren. Daarnaast raken steeds meer mensen ervan doordrongen dat samenwerking leidt tot snellere en betere onderzoeksresultaten en tot een effectievere implementatie van deze uitkomsten.

In dit jaarverslag zullen wij u informeren over onze inspanningen in het voorbije jaar en u vindt hier informatie over het onlangs opgerichte internationale samenwerkingsverband GONet. Uiteraard vermelden we ook welke projecten zijn gestart of afgerond, van welke studies publicaties zijn verschenen en waar voordrachten zijn gehouden.

Juli 2011

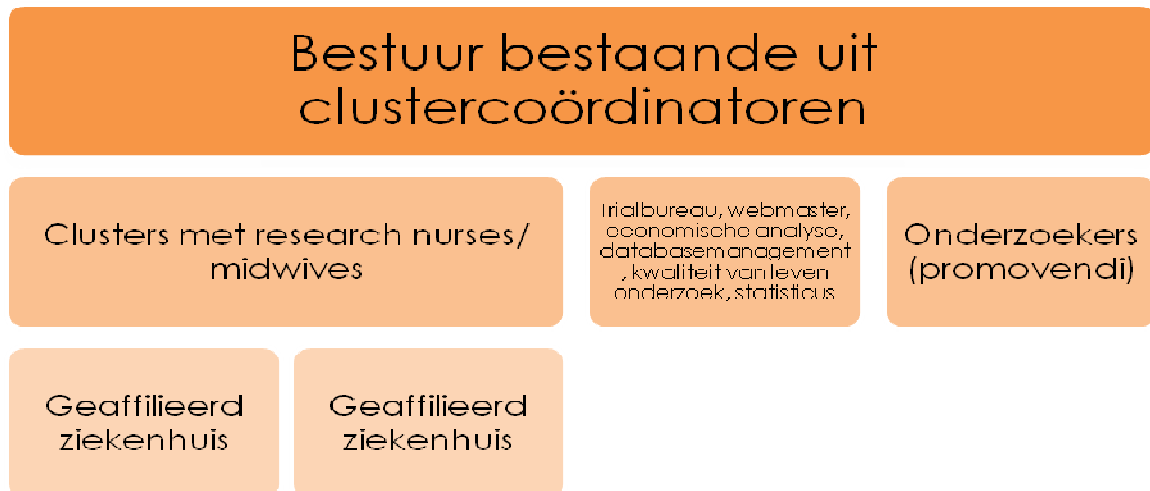
Annemieke Hoek, coördinator consortium voortplantingsgeneeskunde
Jan-Paul Roovers, coördinator consortium urogynaecologie
Judith Huirne, coördinator consortium benigne gynaecologie
Ben Willem Mol, coördinator consortium verloskunde

Mission statement

Hoewel veel klinische handelingen deel uitmaken van de dagelijkse zorg, is er vaak geen wetenschappelijk bewijs of deze behandelingen werken. In de Nederlandse verloskunde en gynaecologie is er sterke variatie tussen en zelfs binnen centra in de keuze van behandeling. De enige manier om dit dilemma op te lossen is het doen van evaluaties in multicentrisch verband. Het is ons doel om deze multicentrische evaluaties uit te voeren, om zo de kwaliteit en de doelmatigheid van zorg te verbeteren.

De kracht van de consortiumstructuur

Het is wellicht niet direct inzichtelijk hoe de consortiumstructuur er precies uitziet en wat nu de meerwaarde van deze structuur is.



Er zijn tien clusters, meestal perinatologische centra met de geaffilieerde ziekenhuizen in de regio. Ieder cluster levert een coördinator, een gynaecoloog die zitting heeft in het consortiumbestuur, research nurses/midwives aanstuurt en de contactpersoon is voor de ziekenhuizen in dat cluster. De research nurses zijn in het hele cluster actief, zij counselen potentiële proefpersonen, zorgen voor data-invoer, verzorgen follow-up, houden presentaties voor de artsen in de ziekenhuizen en zijn betrokken bij het verkrijgen van lokale uitvoerbaarheidverklaringen via de Medisch Ethische Toetsingscommissies (METC's).

Daarnaast is er een centraal Trialbureau dat gesitueerd is in het AMC en verantwoordelijk is voor de informatievoorziening binnen het Consortium, METC-procedures en kwaliteitsverbetering. Ook is het trialbureau de intermediair tussen onderzoekers en de programmeurs die de interface voor de digitale randomisatie en dataverzameling maken. In het AMC en het UMCU wordt verder voor de verschillende consortiumstudies toegezien op de kwaliteit van de data-invoer en wordt ondersteuning geboden bij de data-analyse.

De onderzoekers werken doorgaans grotendeels klinisch en hoeven dankzij de consortiumstructuur maar weinig tijd aan inclusie en de administratieve aspecten van de studie te besteden. Zodoende kunnen zij zich primair richten op de wetenschappelijke en inhoudelijke facetten van hun studie.

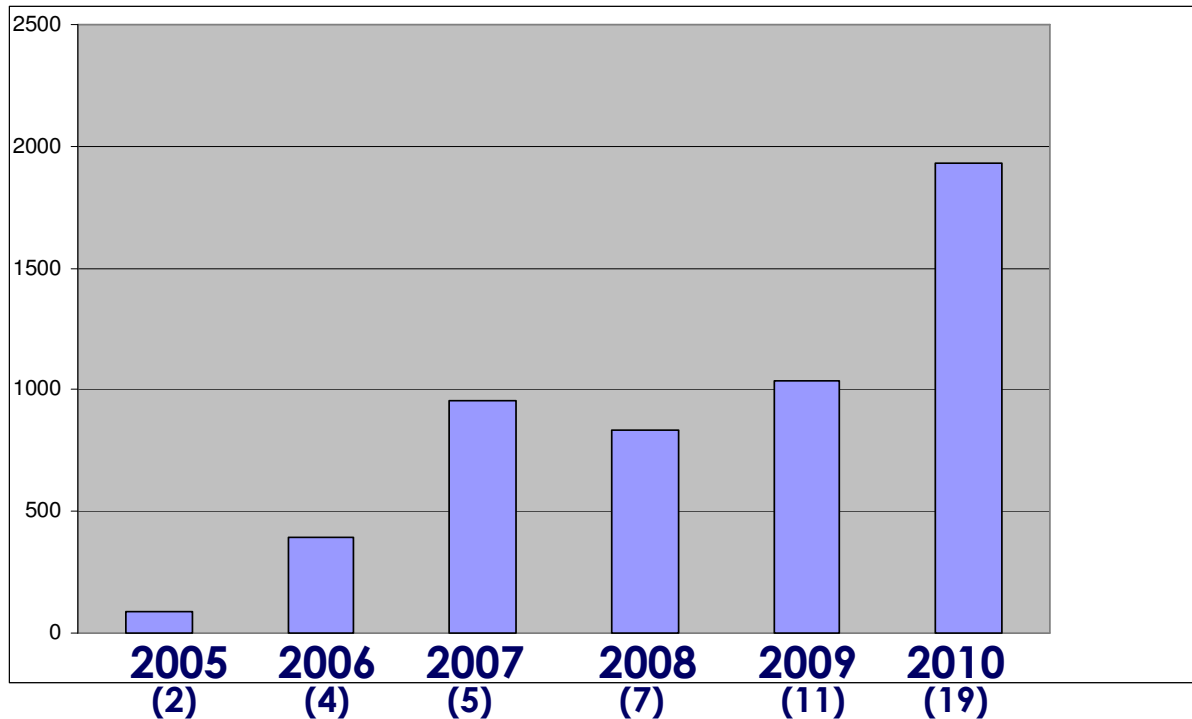
De voordelen van deze organisatie zijn evident: er is een bestaand landelijk netwerk met een geoliede logistiek en professionals die zeer ervaren zijn in hun deel van het totale proces. Dankzij het netwerk zijn de lijnen kort wanneer er gestart wordt met een nieuwe studie; er kunnen in korte tijd veel ziekenhuizen benaderd worden voor deelname, het trialbureau neemt een groot deel van de METC-procedures voor zijn rekening en de research nurses dragen zorg voor een actieve participatie van de centra in de onderzoeken. Beginnende promovendi hoeven niet zelf het wiel uit te vinden, maar kunnen terugvallen op bestaande kennis die al binnen de organisatie aanwezig is.

Ontwikkeling Consortium

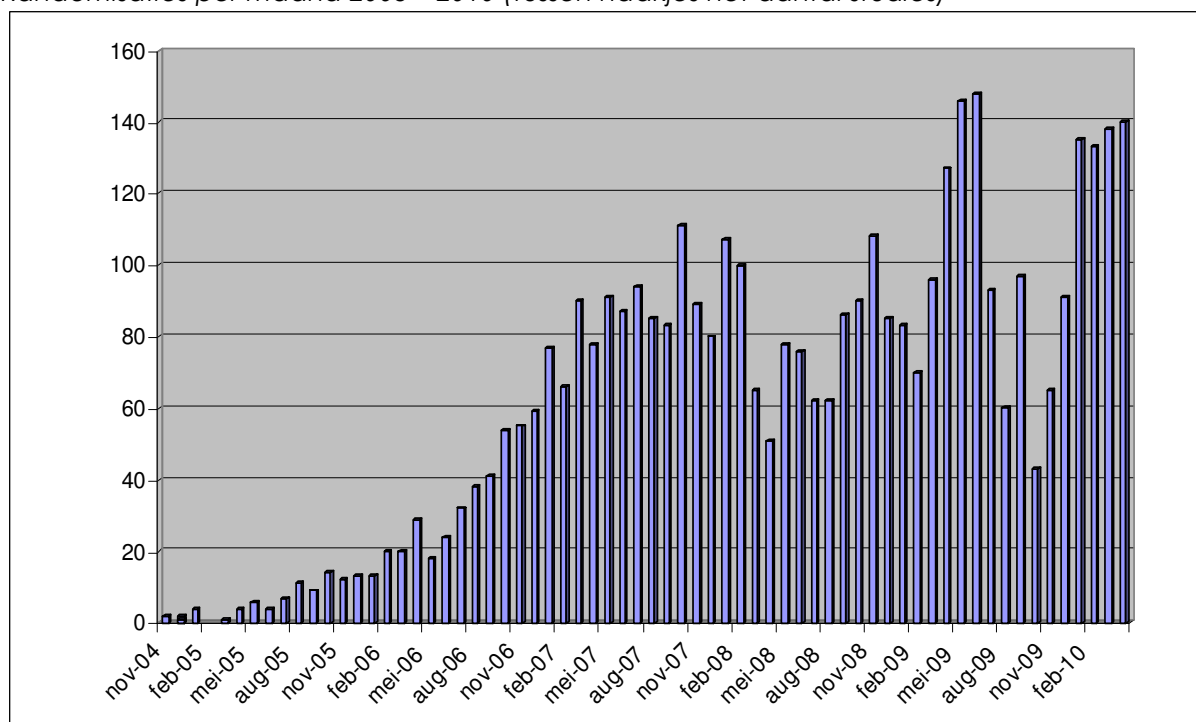
Nadat het aantal centra dat deelnam aan consortiumstudies in de periode van 2005 tot 2009 steeg van 13 naar 73, is aan die groei in 2010 een (voorlopig) einde gekomen. Gezien met name het belang van snelle implementatie van onderzoeksresultaten blijft het ons doel om alle 90 ziekenhuizen in Nederland in het consortium te betrekken.

Ruimte voor groei was en is er zeker nog in het aantal inclusies. Werden er in 2006 nog 350 proefpersonen gerandomiseerd voor alle consortiumstudies tezamen, in 2010 was dit aantal opgelopen tot 1934 (voor de studies op het gebied van verloskunde en voortplantingsgeneeskunde). De randomisaties voor PROBAAT (1200) zijn hierbij buiten beschouwing gelaten; dat waren er zo veel dat meetellen een vertekend beeld zou geven.

Randomisaties per jaar 2005 – 2010 (tussen haakjes het aantal studies)



Randomisaties per maand 2005 – 2010 (tussen haakjes het aantal studies)



Belangrijk is ook de ontwikkeling van de consortia voortplantingsgeneeskunde, benigne gynaecologie en oncologie. De voortplantingsgeneeskunde kreeg een enorme impuls door financiering van de studies Optimist, Insight en In Vitro Maturatie, die prima aansluiten bij lopende studies INeS en Lifestyle. Het streven is om de ondersteunende structuur met researchmedewerkers zoveel mogelijk te integreren voor wat betreft verloskunde, voortplantingsgeneeskunde en gynaecologie. Deze ontwikkeling gaat niet overal even snel, maar in Groningen, Amsterdam, Brabant en Twente vind dit al geïntegreerd plaats. Ook krijgen steeds meer ziekenhuizen een eigen researchmedewerker. Het totaal aantal researchmedewerkers groeide naar 38 in 2011.

Een hoogtepunt in 2010 was de kasteelcursus. Hoewel de buitenlandse sprekers vanwege de IJslandse aswolk niet konden komen, was de 2-daagse meeting met promovendi uit alle subdisciplines van het vakgebied verloskunde/gynaecologie met inbreng van alle 8 faculteiten uniek te noemen.

Chateau Coulon, april 2010



Ook op het gebied van de lange termijn follow-up wordt meer en meer samengewerkt. Omdat de meeste subsidies een looptijd hebben van 3 of 4 jaar, is lange termijn follow-up vaak een ondergeschoven kindje. Dit is niet terecht, want het doel van interventies is natuurlijk gezondheid op lange termijn. Dit geldt zeker voor de verloskunde en de voortplantingsgeneeskunde, waar succes op korte termijn slechts beperkt meetbaar is.

In 2010 geeft zich een follow-up club gevormd, waarbij onderzoekers van een groot aantal projecten samen werken aan de follow-up van hun studies. Dit wordt gesteund door een kleine subsidie van ZonMw. Onmisbaar is hier de expertise van dr. Aleid Wassenaar en prof dr. Anneloes van Baar, die beide hun expertise overbrengen aan de jonge (arts-) onderzoekers.

Naast het feit dat researchnurses en -midwives zich specialiseren in het includeren van patiënten en het verzamelen van gegevens, is ook op het gebied van data-analyse een begin gemaakt met specialisatie. In het Julius Centrum in het UMC Utrecht is Ewoud Schuit die de analyse van diverse trials op het gebied van vroeggeboorte zal doen (AMPHIA, APOSTEL II, ProTWIN). Doordat hij meerdere studies analyseert over eenzelfde probleem, ontwikkelt hij expertise waardoor analyses sneller en beter verlopen. Ewoud is ook betrokken bij Individuele Patiënten Data analyse van internationale studies op het gebied van

vroeggeboortepreventie. In Maastricht krijgt Sander van Kuijk van de PreCare studie mogelijk ook zo'n overkoepelende functie.

In ons vorige jaarverslag werd al gewag gemaakt van de ontwikkeling van een internationaal samenwerkingsverband. In september 2010 is dat formeel tot stand gekomen onder de naam Global Obstetrics Network (GONet). Dit netwerk heeft een website (www.globalobstetricsnetwork.org), wisselt informatie uit over studieplannen en treft voorbereidingen voor gezamenlijke studies en publicaties. Er wordt gewerkt aan vroegtijdige uitwisseling van informatie over te plannen studies, en over gemeenschappelijke eindpunten. De Launch van GONet in februari 2011 tijdens de SMFM in San Francisco was een succes, met zo'n 60 deelnemers.



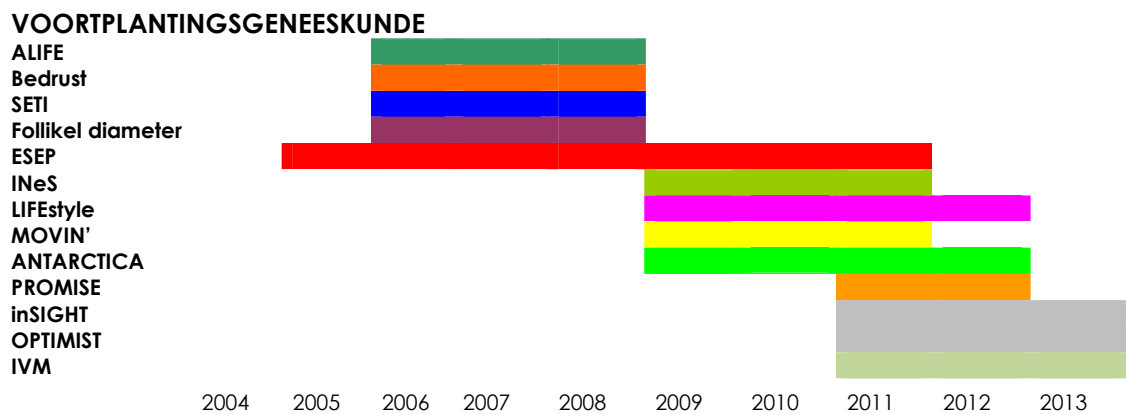
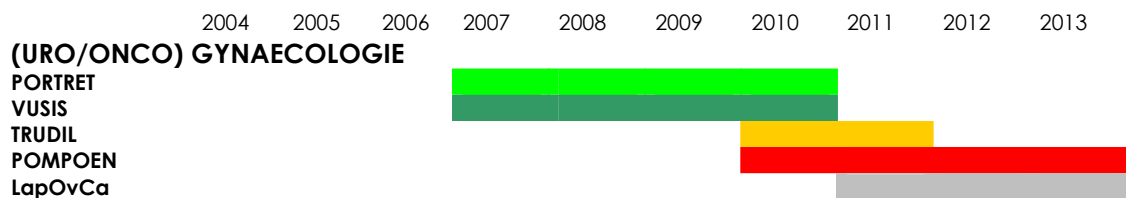
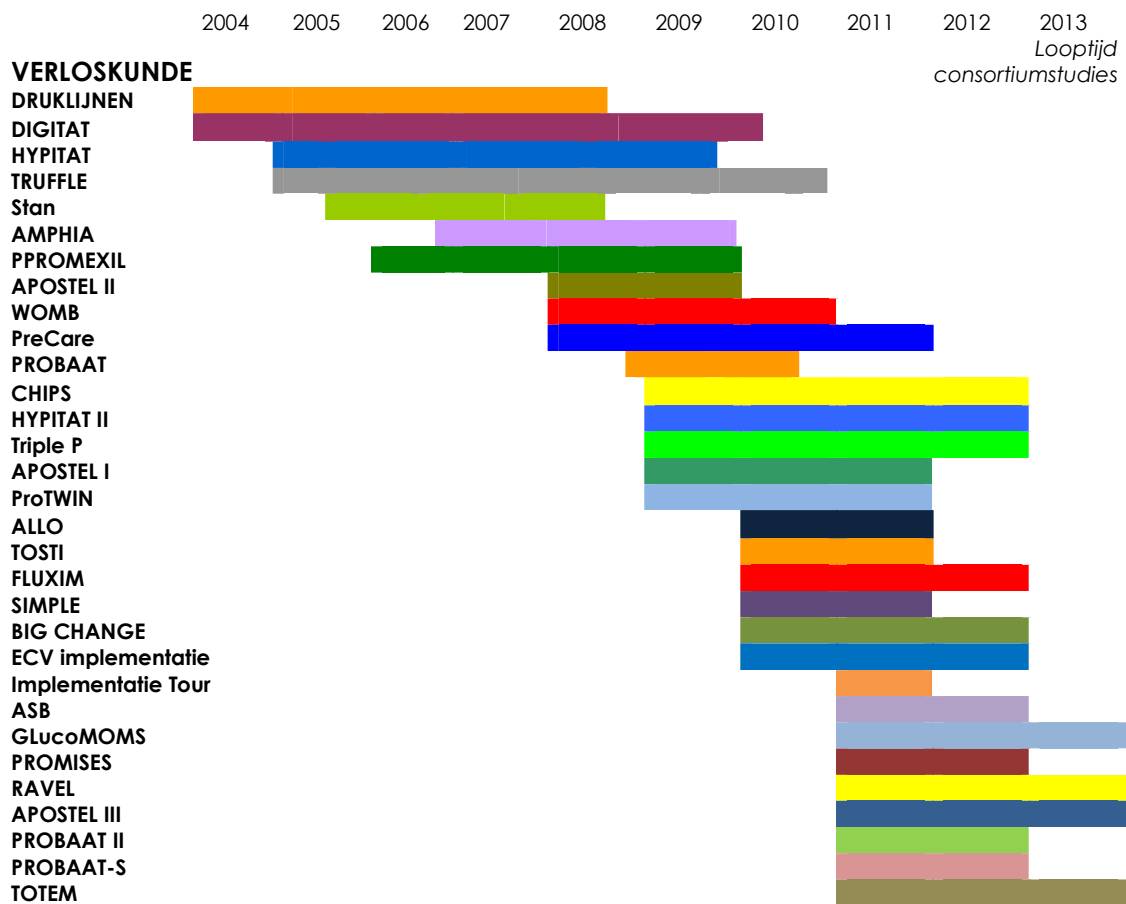
De launch van GONet, februari 2011 met netwerkonderzoekers uit de VS, Canada, Australië, Hong Kong, UK en mainland Europe.

Daarnaast vindt er meta-analyse plaats met individuele patiënten data (IPD) onder andere met de samengevoegde data van zes grote studies uit verschillende landen naar het gebruik van progesteron ter voorkoming van vroeggeboorte bij meerlingzwangerschappen, studies over STan en studies over inleiden of niet bij prematuur gebroken vliezen.

In oktober 2011 vindt er in Washington een conferentie plaats met onderzoekers en subsidiegevers uit 5 landen, met als doel om tot een internationale agendavorming te komen.

Het Consortium doet nu ook mee aan de Canadese CHIPS studie en de Nederlands/Engelse PROMISE trial. Door gecoördineerd te includeren voor deze internationale studies is de Nederlandse bijdrage goed. Bovendien zullen de resultaten van die studies goed toe te passen zijn op de Nederlandse situatie.

Overzicht van de lopende en afgeronde studies



Resultaten

Dat de gezamenlijke benadering werkt, blijkt ook uit de ontvangst van onze studieresultaten. Het is inmiddels gebruikelijk dat afgeronde consortiumstudies worden gepresenteerd op het Gynaecologisch congres. In 2010 werd bekend dat APOSTEL II was geselecteerd als openingspresentatie op het jaarlijkse congres van de Society for Maternal-Fetal Medicine (SMFM) en PROBAAT als vijfde presentatie. Ook in 2010 verschenen publicaties over consortiumstudies in toonaangevende internationale tijdschriften de druklijnenstudie (IUPC) en de ALIFE studie in de New England Journal of Medicine, STan in Obstetrics and Gynecology en DIGITAT in de British Medical Journal. Verschillende consortiumonderzoekers (o.a. Michelle Westerhuis – Stan, Jannet Bakker – IUPC, Wietske Hermes – HyRAS) ontvingen prijzen voor hun werk.

Lopende studies Verloskunde

Naam	ZonMw subsidie	Start	Einde	Totale inclusie	Stadium
PreCare	Ja	2008	2012	300	Inclusie
HYPITAT-2	Ja	2009	2013	400	Inclusie
TOSTI	Ja	2009	2012	16.000	Inclusie
ProTWIN	Ja	2009	2011	660	Inclusie
Triple P Screening	Ja	2009	2012	40.000	Inclusie
Triple P Treat	Ja	2009	2012	1.920	Inclusie
ALLO	Ja	2009	2011	220	Inclusie
APOSTEL I	Ja	2009	2012	220	Inclusie
Implem.ECV	Ja	2009	2012	32 centra	Inclusie
FLUXIM	Ja	2009	2012	320	Inclusie
ASB	Ja	2011	2012	4400	Vorbereiding
PROMISES	Ja	2009	2012	300	Inclusie
GlucO MOMS	Ja	2011	2013	300	Vorbereiding
RAVEL	Ja	2011	2013	1136	Vorbereiding
APOSTEL III	Nee	2011	2014	500	Vorbereiding
PROBAAT II	Nuts-Ohra	2011	2013	1442	Vorbereiding
PROBAAT-S	Nee	2011	2013	1500	Vorbereiding
TOTEM	Nee	2011	2014	1130	Vorbereiding

Voltooide studies Verloskunde

Naam	ZonMw subsidie	Start	Einde	Totale inclusie	Stadium
HYPITAT	Ja	2006	April 2008	750	Lancet, aug. 2009
STan	Ja	2006	Augustus 2008	5700	Obstetrics/Gyn
IUPC	Nee	2004	2008	2000	NEJM, jan. 2010
DIGITAT	Ja	2005	December 2008	650	BMJ, dec. 2010
Truffle	Ja	2005	2011	562	Data analyse
AMPHIA	Ja	2006	Juni 2009	650	Data analyse
PPROMEXIL	Ja	2007	Oktober 2010	725	Lancet?
APOSTEL II	Ja	2008	Februari 2010	400	Data analyse
WOMB	Landsteiner St.	2008	2010	500	Data analyse
HyRAS	Nee	2008	2010	1200	Data analyse
PROBAAT	Nee	2009	2010	1176	Data analyse

Lopende studies voortplantingsgeneeskunde

Naam	ZonMw subsidie	Start	Einde	Totale inclusie	Stadium
ESEP	Ja	2005	2011	450	Inclusie
METEX	Nee	2006	2011	72	Inclusie
INeS	Ja	2009	2012	600	Inclusie
Lifestyle	Ja	2009	2014	530	Inclusie
M-ovin'	Nee	2008	2012	200	Inclusie
TRUST	nee	2009	2012	68	Inclusie
OPTIMIST	Ja	2011	2013	738	Voorbereiding
InSIGHT	Ja	2011	2013	1500	Voorbereiding

Voltooide studies voortplantingsgeneeskunde

Naam	ZonMw subsidie	Start	Einde	Totale inclusie	Stadium
ALIFE	ja	2006	2008	300	NEJM
Bedrust	nee	2005	2007	330	BMJ, 2009
Follikel diameter	nee	2005	2008	200	Data analyse
SETI	nee	2006	2008	120	Data analyse

Lopende studies (uro)gynaecologie

Naam	ZonMw subsidie	Start	Einde	Totale inclusie	Stadium
CUPIDO II	nee	2007	2011	126	Inclusie
POMPOEN	nee	2009	2013	200	Inclusie

Voltooide studies (uro)gynaecologie

Naam	ZonMw subsidie	Start	Einde	Totale inclusie	Stadium
PORTRET	ja	2008	2010	400	Data analyse
VUSIS I	ja	2007	2008	60	Data analyse
VUSIS II	ja	2009	2010	600	Data analyse
TRUDIL	ja	2010	2011	120	Data analyse

Nieuwe gesubsidieerde projecten

In 2010 zijn de volgende projecten voor subsidie gehonoreerd:

ZonMw Doelmatigheid/Effecten en kosten 171102009 Remifentanyl patient-controlled analgesia (RPCA) vs epidural analgesia (EA) during labour, RAVEL studie, Dr. J.M. Middeldorp/ LUMC

ZonMw Doelmatigheid/Effecten en kosten 171102005 Effectiveness of continuous glucose monitoring during pregnancy in women with type 1 and type 2 diabetes, GLuCoMOMS studie, dr. I.M. Evers AMC/UMCU

ZonMw Doelmatigheid/Effecten en Kosten 171102020 The OPTIMIST trial: OPTIMisation of cost effectiveness through Individualised FSH Stimulation dosages for IVF Treatment, dr. F.J. Broekmans UMU

ZonMw Doelmatigheid/Effecten en kosten 171102019 inSIGHT trial SIGNificance of routine Hysteroscopy prior to a First IVF Treatment cycle, dr. F.J. Broekmans UMCU

ZonMw Doelmatigheid/Vroege evaluatie en medische innovatie 171101010 "A randomised controlled trial comparing In Vitro Maturation of oocytes with in vitro fertilisation in women with an increased risk of ovarian hyperstimulation syndrome.", dr. J.P. de Bruin Jeroen Bosch Den Bosch

Samenwerkingsverbanden

Sinds 2006 lopen er twee studies op het gebied van kindergeneeskunde. Ook de kinderartsen werken in eenzelfde infrastructuur. Voorlopig houdt de kindergeneeskunde echter nog de eigen identiteit en wil niet te intensief samenwerken. De afstemming van nieuwe studies die hun eindpunt bij de kindergeneeskunde hadden verliep niet altijd vlot. Daarom is begin 2009 een document opgesteld tussen neonatologen en obstetricki om de onderlinge afstemming te verbeteren. Dit document is geaccordeerd door de obstetricki en door de neonatologen.

In 2009 is de Triple P studie gestart, waarvan het screeningsdeel grotendeels in de eerste lijn wordt uitgevoerd. Er zijn twee promovendi aangesteld op deze studie, een arts en een verloskundige.

Naast het Verloskundig Consortium zijn er nu ook het Urogynaecologisch Consortium en het Consortium voortplantingsgeneeskunde gevormd. Deze hebben een clusterindeling en een infrastructuur die veel lijkt op die van het verloskundig onderzoeksconsortium. Veel research nurses zijn voor meerdere consortia actief. In 2010 is ook begonnen met een consortium benigne gynaecologie, dat in 2011 zal samengaan met het Urogynaecologisch Consortium. Zo ontstaan 3 platforms, waarbinnen in netwerkverband grote studies worden verricht.

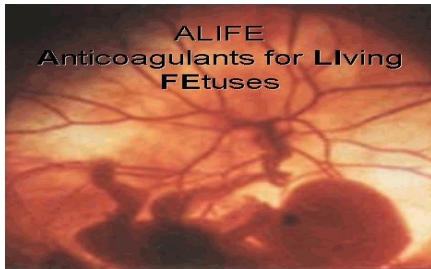
Vanuit het ministerie van VWS is voor de periode 2008-2012 geld beschikbaar gekomen voor perinatologische audit. Bij de perinatologische audit worden de casussen waarbij ernstige complicaties zijn opgetreden, uitgebreid besproken. Per regio is op de werkvloer gemiddeld één à twee dagen ondersteuning nodig. De consortiumorganisatie leent zich hier bij uitstek voor. Inmiddels maken vrijwel alle regio's in Nederland voor de perinatale audit gebruik van medewerkers van het consortium.

Implementatie

In 2010 zijn alle voorbereidingen getroffen voor de Implementatie Tour. Door dr. M. van Pampus is een ZonMw subsidie verkregen om de resultaten van meerdere afgeronde Consortiumstudies gezamenlijk actief onder de aandacht te brengen van gynaecologen, verloskundigen, arts-assistenten en verpleegkundigen in heel Nederland. In 2011 zullen de research nurses en midwives en gynaecologen van het Consortium het land in trekken om informatie te geven over de uitkomsten van onze studies. Het doel is dat daarbij de medewerkers van alle Nederlandse ziekenhuizen bereikt worden opdat de nieuwe kennis snel geïmplementeerd kan worden.

Voltooid studies

ALIFE



Promovendus Drs. S. Kaandorp
Project leaders Dr. M. Goddijn, dr. S. Middeldorp,
ZonMw 94527003
Nederlands Trial Register: NTR206

A randomized placebo controlled trial for women with recurrent miscarriage without an apparent cause.

Summary

To assess the efficacy of two different anticoagulant strategies, as compared with placebo, on the live-birth rate in women with unexplained recurrent miscarriage, with or without an inherited thrombophilia, we conducted a randomized prospective multicentre open label trial, double blinded and placebo controlled for Aspirin.

Intervention and follow-up

The three intervention groups are as follows: placebo and aspirin are double blinded, the third group is open label and combines aspirin with low molecular weight heparin (LMWH). Placebo and Aspirin are packed in identical sachets and favourably started preconceptionally and continued until 36 weeks of gestation. In the third group, Aspirin will be combined with LMWH (nadroparin 2850 EH/day) as soon as a vital intrauterine pregnancy is diagnosed. LMWH will be continued throughout the pregnancy until 12 hours before labour.

Results

Between February 2004 and January 2008, 364 women were included in the trial. The live birth rate did not differ between women assigned to aspirin combined with LMWH, aspirin alone and placebo, 54.5%, 50.8% and 57.0%. In 299 women who became pregnant, the live birth rates were 69.1%, 61.6%, and 67.0% (reference) respectively. Side effects, most notably skin reactions, occurred more often in women assigned to aspirin and nadroparin.

Conclusions

Aspirin combined with LMWH and aspirin alone did not improve live birth rate relative to placebo in women with unexplained recurrent miscarriage. (Current Controlled Trial number, ISRCTN58496168)

Presentations

Oral presentation and press conference, American Society of Hematology, 7-12-2009 New Orleans, United States of America.

Oral presentation, Dutch Gynaecology Congress, 4-06-2010, Breda, The Netherlands.

Oral presentation, European Society of Human Reproduction and Embryology, 28-06-2010 Rome, Italy.

Publication

Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyák K, Mol BW, Folkeringa N, Nahuis M, Papatsonis DN, Büller HR, van der Veen F, Middeldorp S. Aspirin plus Heparin or Aspirin Alone in Women with Recurrent Miscarriage. *N Engl J Med.* 2010 Apr 29;362(17):1586-96. Epub 2010 Mar 24. PMID: 20335572

AMPHIA



Promovendus: Arianne Lim, AMC Amsterdam/ UMC Utrecht

Projectleider: Prof. Dr. H.W. Bruinse, UMC Utrecht

Clinical trials register ISRCTN 40512715 **ZonMw** 62200019

17-Alpha hydroxyprogesterone in Multiple pregnancies to Prevent Handicapped Infants

Objective To investigate the hypothesis that prophylactic administration of 17 alpha hydroxyprogesterone (17OHPC) will reduce the incidence of the composite neonatal morbidity by reducing the early preterm birth rate in twin pregnancies. The composite morbidity rate after early preterm delivery between 24-27, 28-32 and 32-34 weeks of gestation is respectively 77%, 35% and 12%. After 34 weeks it sharply declines to less than 2%. The incidence of preterm birth in twins in these gestational periods is 1.8, 5.2 and 7.4%, respectively. As a result of this early delivery finally about 8% of the children will die, 6% will remain severely disabled and 20% will be moderately disabled. At present, no general accepted strategy for prevention of preterm birth in multiple pregnancies exists. Prophylactic administration of 17OHPC that proved to be effective in singleton pregnancies at high risk for preterm delivery is as yet not advised.

Study design: Randomised placebo controlled trial.

Study population: Women with a multiple pregnancy (bichorionic or monochorionic) at a gestational age between 15 and 20 weeks of gestation.

Intervention: Weekly 250 mg 17 OHPC i/m injections from 16-20 weeks up to 36 weeks of gestation versus placebo.

Outcome measures: Primary outcome is composite bad neonatal condition (death or severe morbidity). Secondary outcome measures are time to delivery, preterm birth rate before 32 and 37 weeks, days of admission in neonatal intensive care unit, maternal morbidity, maternal admission days for preterm labour and costs.

Power/ data analysis: Analysis will be by intention to treat. The effectiveness of progesterone versus placebo will be assessed by calculating relative risks and 95% confidence intervals. Assuming a decrease of the incidence of bad neonatal outcome from 14.9% without to 7.9% with progesterone, using a two sided test with an alpha 0.05 and a beta of 0.8, 700 women (350 per arm) are needed in the study.

Time schedule: Three months for logistics of the study set up, 30 months for recruitment and seven months for the final data collection and evaluation.

Trial end: August 2009. 672 inclusions

Remarks: The AMPHIA study group has initiated an individual patient data Meta-analysis involving 7 international multicentre trials involving more than 3000 patients.

Publications

Lim AC, Mol BWJ, Bruinse HW. *Progesteron ter preventie van vroeggeboorte: de stand van zaken.* Nederlands Tijdschrift voor Geneeskunde. 2010;154:A1730.

Lim AC, Bloemenkamp KWM, Boer K, Duvekot JJ, Erwich JJHM, Hasaart THM, Hummel P, Mol BWJ, Offermans JPM, van Oirschot CM, Santema JG, Scheepers HCJ, Schols W, Vandenbussche FPHA, Wouters MGAJ, Bruinse HW. *Progesterone for the prevention of preterm birth in women with multiple pregnancies: the AMPHIA trial.* BMC Pregnancy Childbirth. 2007 Jun 19;7:7

Lim AC, Bruinse HW, AMPHIA projectgroep. *Het voorkómen van vroeggeboorte bij meerlingen: de AMPHIA-studie.* Nederlands Tijdschrift voor Obstetrie en Gynaecologie 2006;119:24-25

Presentations

Lim AC, Schuit E, on behalf of the AMPHIA project group. *Mid-pregnancy cervical length as a predictor of preterm birth in multiple pregnancies*. Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. Februari 2011. Poster presentation.

Lim AC, Schuit E, on behalf of the AMPHIA project group. *Mid-pregnancy cervical length and the risk of cesarean delivery in multiple pregnancies*. Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. Februari 2011. Poster presentation.

Lim AC. *Prevention strategies for premature delivery with multiple pregnancy? Facts and fiction*. International Congress on Twin Studies, Seoul. Juni 2010. Oral presentation.

Lim AC, namens de AMPHIA projectgroep. *Is cervixlengte in het tweede trimester een voorspeller voor het effect van 17-alpha hydroxyprogesteron caproaat op neonatale morbiditeit in meerlingzwangerschappen? Resultaten van de AMPHIA-trial*. Gynaecongres, Breda. Juni 2010. Oral presentation.

Lim AC, Hummel P, Papatsonis D, Hasaart THM, van Oirschot CM, van Eijck J, Porath MM, Kleiverda G, de Graaf IM, van Ginkel AA, Mol BWJ, Bruinse HW. *The effect of 17-alpha hydroxyprogesterone caproate on cervical length in multiple pregnancies*. Society for Gynecologic Investigation Annual Meeting, Orlando. Maart 2010 / Gynaecongres, 3-4 juni 2010. Poster presentation.

Lim AC, namens de AMPHIA projectgroep. *Voorlopige resultaten van de AMPHIA-trial*. Pijlerdag Koepel Foeto-Maternale Geneeskunde NVOG, Nieuwegein. April 2010. Oral presentation.

Lim AC for the AMPHIA study group. *Is second trimester cervical length a predictor for an effect of 17-alpha hydroxyprogesterone caproate on neonatal morbidity in multiple pregnancies? Preliminary results from the AMPHIA-trial*. Society for Gynecologic Investigation Annual Meeting, Glasgow. Maart 2010. Poster presentation.

Lim AC, Mol BW, Bruinse HW voor de AMPHIA studiegroep. *Preventie van spontane vroeggeboorte: progesteron, een update*. Gynaecongres, Utrecht. Juni 2009. Oral presentation.

Mol BW, namens de AMPHIA projectgroep. *Plaats van progesteron bij de preventie van vroeggeboorte*. Congres Obstetrie, Gynaecologie en Fertiliteit Anno 2008, Rotterdam. April 2008. Oral presentation.

Lim AC. *Progesteron ter preventie van vroeggeboorte*. Refereeravond Gynaecologie / Verloskunde cluster Enschede. Januari 2008. Oral presentation.

Lim AC. *Progesteron ter preventie van vroeggeboorte*. Werkgroepvergadering Perinatologie en Maternale Ziekten NVOG, Utrecht. November 2007. Oral presentation.

APOSTEL II



Promovendus: Carolien Roos, Radboud Nijmegen
Projectleider: Prof. dr. F. Lotgering Radboud Nijmegen/ Prof. dr. J. van der Post AMC
Clinical trials register NTR 1336
ZonMW 170885601

Assessment of Perinatal Outcome after Sustained Tocolysis in Early Labour

Objective

It is evident that tocolysis with administration of corticosteroids is effective for 48 hours. At present, no unanimity exists among obstetricians, regarding benefits of sustained tocolysis. On the one hand, tocolytics maintenance therapy with calcium channel blockers might be beneficial due to its positive effect on gestational age. On the other hand, its use of tocolytics is related to severe side effects for mother and child. Moreover, prolongation of pregnancy might also increase the chance for perinatal complications such as infection.

Study design

Multicentre randomised placebo-controlled trial. The study will be performed within a consortium of ten perinatal centres, which are collaborating in several proposed studies. Study population: women with a gestational age between 24 and 31⁺⁶ weeks who have been treated with tocolysis and steroids for preterm birth for 48 hours are eligible for the trial.

Inclusion criteria:

Gestational age between 26 and 32⁺² weeks
Diagnosis of threatened preterm birth
Treatment with tocolysis according to local protocol for 48 hours
Completed course of corticosteroids

Exclusion criteria:

Signs of intrauterine infection
Signs of fetal distress
Placenta praevia
Maternal disease (i.e. severe preeclampsia, HELLP syndrome)
Maternal hypertension
Contra-indication for use of nifedipine

Intervention

Treatment with 80 mgs Nifedipine or placebo for 12 days.

Outcome measures

Main outcome will be neonatal mortality, neonatal morbidity (severe respiratory distress syndrome, bronchopulmonary dysplasia, severe intraventricular haemorrhage more than grade 2, periventricular leucomalacia more than grade 1, proven sepsis, necrotising enterocolitis) and birth weight. Secondary outcome will be gestational age at delivery, days on supported ventilation, days on additional oxygen, days in NICU, total days in hospital until 3 months corrected age, costs.

Power/data analysis

The analysis will be by intention to treat. A difference in reduction of compound morbidity from 25% to 15%, with beta of 0.2 and alpha of 0.05 can be detected if 400 patients can be analysed (200 in each arm).

Trial end: January 2010, 406 randomisations

Remarks: The study was presented at the Society for Maternal Fetal Medicine in the plenary session as number #1 abstract

Publications

C.Roos, L.Scheepers, K.Bloemenkamp, A.Bolte, J.Cornette, J.Derks, H.Duvekot, J.van Eyck, J.Kok, A.Kwee, A.Merién, B.Opmeer, M.van Pampus, D.Papatsonis, M.Porath, J.van der Post, S.Scherjon, K.Sollie, M.Spaanderman, S.Vijgen, C.Willekes, B.W.Mol, F.Lotgering. Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour. BMC Pregnancy and Childbirth Study Protocol, 9:42

Presentations

Roos C, namens de APOSTEL II projectgroep: *Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour*. Gynaecongres, Breda, The Netherlands, June 4th 2010. Oral presentation.

Roos C, namens de APOSTEL II projectgroep: *Prediction of labour within 7 days in women admitted for threatened preterm labour*. Gynaecongres, Arnhem, The Netherlands, November 11th 2010. Oral presentation.

Roos C, Spaanderman M, Bloemenkamp K, Bolte A, Cornette J, Duvekot H, Van Eyck J, Kok J, Kwee A, Merién A, Opmeer B, Oudijk M, Van Pampus M, Papatsonis D, Porath M, Scheepers L, Scherjon S, Schuit E, Sollie K, Vijgen S, Willekes C, Mol BW, Van der Post J, Lotgering F: *Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour*. Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. February 2011. Oral presentation.

Vis J, Roos C, Van Straalen J, Bloemenkamp K, Bolte A, Cornette J, Duvekot H, Van Eyck J, Kok J, Kwee A, Merién A, Opmeer B, Oudijk M, Van Pampus M, Papatsonis D, Porath M, Van der Post J, Scheepers L, Scherjon S, Schuit E, Sollie K, Spaanderman M, Willekes C, Lotgering F, Mol BW: *Does fibronectin status influence the effectiveness of sustained tocolysis in women with threatened preterm labour?* Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. February 2011. Poster presentation.

Bedrust studie

Promovendus: Inge Custers, AMC Amsterdam

Projectleider: Prof. Dr. BW Mol AMC

Trial registration Current Controlled Trials ISRCTN53294431

15 minutes bedrest or immediate mobilisation after IUI

Background

Different variables in the IUI procedure have been well investigated: semen preparation techniques (gradient, swim-up or wash and centrifugation), IUI in natural versus stimulated cycles and single versus double insemination. One of the issues that remains unresolved is the question whether after insemination the patient can immediately mobilize or should stay in supine position for a short period of time. Several studies have investigated sperm migration and survival in the female genital tract. Spermatozoa may reach the fallopian tube - the site of fertilization - within 2 to 10 minutes. In IUI the sperm is deposited directly inside the uterine cavity, and therefore close to the site of fertilisation. This suggests that sperm migration to the site of fertilization is independent of the position of the female directly after IUI. In 2000 however, Saleh et al reported a significantly increased cumulative pregnancy rate per IUI-cycle and per couple in favour of women staying in supine position for 10 minutes after IUI as compared to immediate mobilization. Unfortunately, this randomized controlled trial was underpowered and unbalanced. Therefore the effect of "bed rest" after IUI remains unclear.

Objective

Our objective is to answer the question whether a short time of immobilization (i.e. 15 minutes) has a potential advantage on pregnancy rates after intra-uterine insemination, over immediate mobilization and outweighs the disadvantage of the extra time and working space it consumes.

Study design It is a multi centre randomised controlled trial.

Population

All patients, above 18 years of age, receiving IUI with fresh or cryo-preserved donor- or husband's sperm and IUI with or without controlled ovarian hyper stimulation (IUI-COH), as a treatment for their subfertility will be eligible for the trial.

Intervention and follow-up

Intra uterine insemination will be performed in spontaneous cycles as well in cycles with controlled ovarian hyperstimulation (COH). Insemination will be performed in lithotomy position with Trendelenburg tilt. After the insemination has been performed, the patient will, according to their allocation, immediately stand up and go home, or will return to normal supine position, and remain so for 15 minutes. Follow up of each included patient will be until 3 cycles of IUI, or in case of pregnancy, until 12 weeks of gestation.

Outcome measures and analysis

The analysis will be performed according to the intention to treat principle. The primary outcome measure is ongoing pregnancy per couple. Primary and secondary outcome measures will be expressed in pregnancy rates per couple and relative risks with 95% confidence intervals. With use of life-table analysis (Kaplan-Meier curves) the cumulative probability of pregnancy will be estimated in the two groups. The treatment effect will be expressed as a hazard ratio. Measures for uncertainty will be expressed using 95% confidence intervals. Using an alpha-error of 0.05 and a beta-error of 0.20, and assuming a drop-out rate of 10%, 185 couples are needed in each arm to judge whether bed rest is superior over immediate mobilisation.

Publications

Custers IM, Flierman PA, Maas P, Cox T, van Dessel HJM, Gerards MH, Mochtar MH, Janssen CAH, Van der Veen F, Mol BW. Immobilisation versus immediate mobilisation after intra-uterine insemination; a randomised controlled trial. *BMJ*. 2009;339:b4080.



Disproportionate Intrauterine Growth Intervention Trial At Term

Objective

Small babies with intrauterine growth failure are at increased risk of direct adverse neonatal outcome. In The Netherlands, >9.000 women deliver a baby below the 10th birth weight percentile (SGA). At present, no unanimity exists among obstetricians, regarding benefits of induction of labour to realise earlier delivery or waiting for spontaneous delivery. Induction may result in complications during delivery; expectant monitoring provides a maximal chance of spontaneous labour, however at the expense of possible complications for the child. Both strategies might have impact on maternal quality of life, and there is no reliable information whatsoever on the costs of both strategies.

Study design: Multicentre prospective randomised controlled trial. The study will be performed within a consortium of eight perinatal centres that are collaborating in several proposed studies.

Study population: Women are eligible for the study if they carry a singleton SGA foetus (in cephalic position) at 36 completed weeks (or more).

Intervention: Induction of labour at 35 completed weeks or later (intervention protocol) or expectant monitoring. In case of expectant monitoring, vital parameters of the child will be monitored until the onset of spontaneous labour or until there are signs of an intra-uterine distress (expectant monitoring group).

Outcome measures

Main outcome will be a composite bad neonatal outcome defined as foetal death, a 5 minute Apgar score below 7, an umbilical artery pH below 7.05 and/or admission to the neonatal intensive care. Secondary outcomes will be severe maternal morbidity, maternal quality of life and costs.

Power/data analysis

Based on an incidence of 15% of poor neonatal outcome, we need 275 patients in each arm to exclude large difference between neonatal outcome (power 50% to exclude a difference larger than 5%. In case of equivalent maternal and neonatal outcome, the study will compare quality of life of the mother and costs. Assuming an average difference in cost of €1.000 per patient to be relevant, we will need 626 women to be randomised (313 per arm). Thus, the study aims to recruit 626 patients.

Economic evaluation

For each of the two strategies, we will calculate costs of perinatal care. In case of equal neonatal and maternal outcome the analysis will be a cost-minimisation analysis.

Trial end: December 2008, 650 randomisations

Key publication

Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, van der Salm PC, van Pampus MG, Spaanderman ME, de Boer K, Duvekot JJ, Bremer HA, Hasaart TH, Delemarre FM, Bloemenkamp KW, van Meir CA, Willekes C, Wijnen EJ, Rijken M, le Cessie S, Roumen FJ, Thornton JG, van Lith JM, Mol BW, Scherjon SA; DIGITAT study group. *BMJ*. 2010 Dec 21;341:c7087. doi: 10.1136/bmj.c7087.

Other Publications

Labour and neonatal outcome in small for gestational age babies delivered beyond 36+0 weeks: a retrospective cohort study. Boers KE, van der Post JA, Mol BW, van Lith JM, Scherjon SA. *J Pregnancy*. 2011;2011:293516. Epub 2010 Dec 15.

Maternal health-related quality of life after induction of labor or expectant monitoring in pregnancy complicated by intrauterine growth retardation beyond 36 weeks. Bijlenga D, Boers KE, Birnie E, Mol BW, Vijgen SC, Van der Post JA, De Groot CJ, Rijnders RJ, Pernet PJ, Roumen FJ, Stigter RH, Delemarre FM, Bremer HA, Porath M, Scherjon SA, Bonsel GJ. *Qual Life Res*. 2011 Apr 6. [Epub ahead of print]

Disproportionate Intrauterine Growth Intervention Trial At Term: DIGITAT. Boers KE, Bijlenga D, Mol BW, LeCessie S, Birnie E, van Pampus MG, Stigter RH, Bloemenkamp KW, van Meir CA, van der Post JA, Bekedam DJ, Ribbert LS, Drogdrop AP, van der Salm PC, Huisjes AJ, Willekes C, Roumen FJ, Scheepers HC, de Boer K, Duvekot JJ, Thornton JG, Scherjon SA. *BMC Pregnancy Childbirth*. 2007 Jul 10;7:12.

Presentations

Boers et al. *DIGITAT study* Annual Meeting, Chicago. February 2010. Oral presentation. Plenary session; abstract number 4.

Gynaecongres June 2009. Boers et al. *DIGITAT study* Oral presentation.

IUPC

Promovendus: J.J.H. Bakker MSc. AMC

Projectleiders: Dr. J. van der Post, dr. B.W. Mol, AMC

Trial register NTR 285

Intra Uterine Pressure Catheter

Objective

In The Netherlands, approximately 10.000 deliveries are induced and 15.000 deliveries are augmented with intravenous oxytocin each year (LVR 2, 2002). The guideline of the Dutch Society of Gynaecology and Obstetricians advises to use an intra uterine pressure catheter (IUPC) to monitor frequency and strength of contractions. (NVOG-richtlijn no5: Inleiden van de baring, February 1997. www.nvog.nl) There is however no scientific evidence that monitoring contractions with IUPC is beneficial in terms of maternal or fetal outcome and whether it is cost effective. The aim of our study is to evaluate the effectiveness of IUPC in comparison to external monitoring during induction of labour.

Study design

Multicentre prospective randomised controlled trial. The study will be performed within a consortium of five perinatal centres, which are collaborating in several proposed studies.

Study population

Women are eligible for the study if labour is induced or augmented with intravenous oxytocin.

Intervention

Women will be at random allocated to placement of an IUPC (intervention group) or external uterine activity monitoring (control group). There will be stratified for centre, parity and induction or augmentation.

Outcome measures

Main outcome will be the neonatal condition defined as a 5 minute Apgar score below 7, an umbilical artery pH below 7.05 and/or admission to the neonatal intensive care. Secondary outcomes will be complications, the number of instrumental deliveries, i.e. caesarean sections and/or assisted vaginal delivery, need for antibiotics by mother or child, total amount of oxytocin used, time to delivery and costs.

Study completed. 1456 patients included.

Publication

Bakker JJH, Verhoeven CJM, Janssen PF, van Lith JM, van Oudgaarden ED, Bloemenkamp KWM, Papatsonis DNM, Mol BWJ, van der Post JAM. Outcomes after Internal versus External Tocodynamometry for Monitoring Labor. N Engl J Med 2010; 362:306-13.

Presentation

Bakker JJH Gynaecongres 2009 IUPC studie

HYPITAT



Promovendi: Corine Koopmans, UMC Groningen
Karin van der Tuuk, UMC Groningen
Projectleider: Dr. M.G. van Pampus, UMC Groningen
Clinical trials register ISRCTN08132825
ZonMw 945-06-553

Hypertension and Pre-eclampsia Intervention Trial At Term

Objective

10% to 15% of all pregnancies are complicated by hypertensive disorders, i.e. pregnancy induced hypertension or pre-eclampsia (19.000 women per year in The Netherlands). The large majority of these cases occur at term. There is no causal treatment but termination of pregnancy. In case of pre-term pregnancies complicated by hypertension, conservative management is advocated as long as the risks for the mother are acceptable. However, there is no consensus whatsoever on the question in such cases at term. Induction of labour might prevent maternal and neonatal complications, but it is also thought to increase the instrumental delivery rate. Nothing is known about the impact of both policies on the psychological well-being of the mother, as well as the costs of both. In The Netherlands in 2002, labour was induced in 9.000 women with pregnancy induced hypertension or pre-eclampsia, whereas labour started spontaneously in 10.000 women.

Study design

Multicentre prospective randomised controlled trial.

Study population

Women with a singleton pregnancy and pregnancy-induced hypertension or pre-eclampsia with a gestational age between 36 0/7 weeks and 41 0/7 weeks.

Intervention

Induction of labour, if necessary preceded by artificial cervical ripening versus expectant monitoring.

Outcome measures

Since we know from large non-randomised data that equality in maternal and neonatal health outcome can be anticipated, this study will have maternal quality of life, quality of recovery and costs as main outcomes. The SF-36 will, among other quality of life measures, be the primary outcome. Of course, maternal and neonatal mortality and morbidity will be measured.

Power/data analysis

The analysis will be by intention to treat. We need two groups of 250 patients to detect relevant differences in the SF-36 (primary outcome). In anticipation of equivalence in quality of life, and maternal and neonatal outcome, the economic analysis will be a cost-minimisation analysis. For each of the two strategies, we will calculate costs of perinatal care for mother and child.

Trial end

March 2008, 755 randomisations

Remarks

The results of the HYPITAT study have led to an adaption of the UK based NICE guidelines, and have lead to immediate changes in policy in the Netherlands, the UK, Canada, the United States and Australia. Awarded with the Zuspan award for best abstract, International Society of Studies on Hypertension in Pregnancy. Washington September 2008.

Key Publication

Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, van Beek E, Bekedam DJ, van den Berg PP, Burggraaff JM, Birnie E, Bloemenkamp KW, Drogdrop AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, le Cessie S, van Loon AJ, van der Post JA, Roumen FJ, Scheepers HC, Spaanderman ME, Stigter RH, Willekes C, Mol BW, van Pampus MG. Induction of labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the HYPITAT trial. *Lancet* 2009;374:979-88.

Other Publications

van der Tuuk K, Koopmans CM, Groen H, Aarnoudse JG, van den Berg PP, van Beek JJ, Copraij FJA, Kleiverda GMD, Porath M, Rijnders RJP, van der Salm PCM, Santema JG, Stigter RH, Mol BWJM, van Pampus MG. Prediction of progression to severe disease in women with gestational hypertension or mild preeclampsia at term. Submitted to ANZJOG.

Koopmans CM, Zwart JJ, Groen H, Bloemenkamp KWM, Mol BWJ, van Pampus MG, van Roosmalen J. Risk indicators for eclampsia in women with gestational hypertension or mild preeclampsia at term: a case-control study. *Hypertens Pregnancy*. 2010 Sep 7 [Epub ahead of print].

Vijgen SMC, Koopmans CM, Opmeer BC, Groen H, Bijlenga D, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KWM, Drogdrop AP, Franx A, de Groot CJM, Huisjes AJM, Kwee A, van Loon AJ, Lub A, Papatsonis DNM, van der Post JAM, Roumen FJME, Scheepers HCJ, Stigter RH, Willekes C, Mol BWJ, van Pampus MG. An economic analysis of induction of labor and expectant monitoring in women with gestational hypertension or preeclampsia at term (HYPITAT trial). *BJOG*. 2010 Sep 14 [Epub ahead of print].

Bijlenga D, Koopmans CM, Birnie E, Mol BWJ, Van der Post JAM, Bloemenkamp KWM, Scheepers HC, Willekes C, Kwee A, Heres MH, van Beek E, van Meir CA, van Huizen ME, van Pampus MG, Bonsel GJ. Quality of life after induction of labor or expectant monitoring in gestational hypertension or preeclampsia at term. *Hypertens Pregnancy*. In press.

Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KWM, Drogdrop AP, Franx A, de Groot CJM, Huisjes AJM, Kwee A, van Loon AJ, Lub A, Papatsonis DNM, van der Post JAM, Roumen FJME, Scheepers HCJ, Willekes C, Mol BWJ, van Pampus MG. Liever inleiden dan afwachten bij aterm zwangerschapshypertensie en milde preëclampsie: de HYPITAT studie. *NTvG*, 2010 (154), nummer 22.

Koopmans CM, Bijlenga D, Aarnoudse JG, van Beek E, Bekedam DJ, van den Berg PP, Burggraaff JM, Birnie E, Bloemenkamp KWM, Drogdrop AP, Franx A, de Groot CJM, Huisjes AJM, Kwee A, le Cessie S, van Loon AJ, Mol BWJ, van der Post JAM, Roumen FJME, Scheepers HCJ, Spaanderman MEA, Stigter RH, Willekes C, MG van Pampus. Induction of labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the Hypitad trial. *BMC pregnancy Childbirth*, July 2007;7:14

Koopmans CM, Van Pampus MG. HYPITAT: 'Hypertension and Preeclampsia Intervention Trial At Term'. *Inleiden of afwachten? NTOG*. 2006;119:28-9

HyRAS



Promovendus Drs. W. Hermes, Leids UMC
Project leader Dr. C.J.M. de Groot, gynecologist,
MCH Westeinde Den Haag
Subsidy: Nuts/Ohra stichting **Trial nummer:** nvt

Background

Secondary prevention of cardiovascular disease (CVD) is difficult, partly due to the lack of an effective strategy to identify individuals at high risk, at an age young enough to benefit from preventive interventions. This study follows a high risk strategy, using the novel concept of pregnancy as a cardiovascular challenge test. Ten to fifteen percent of pregnant women experience gestational hypertension (GH) or preeclampsia (PE) at term. These women have been demonstrated to be at increased risk to develop CVD later in life.

Aims

(I) To screen women who have experienced GH or PE at term for risk factors for CVD, two years after their complicated pregnancy. (II) To estimate the 10-year cardiovascular event risk in these women using validated prediction algorithms, in order to establish the proportion that is likely to benefit from preventive interventions, according to widely accepted guidelines.

Design, setting, and participants

Case control study in the 35 Dutch hospitals participating in the nationwide HYPITAT-study. Participants will be 1200 women of Dutch and foreign origin.

Procedures

Age, ethnicity, smoking status, antihypertensive medication, parental history of (premature) cardiovascular events, systolic blood pressure, body height, body weight, and waist and hip circumference, and fasting levels of total plasma cholesterol, HDL cholesterol, triglycerides, hs CRP, insulin, glucose, and HbA1c and microalbuminuria will be determined two years after pregnancy. Individual 10-year cardiovascular event risks will be estimated using the Adult Treatment Panel III risk score, Reynolds Risk Score and QRISK.

Knowledge transfer

Design of a future intervention study, to evaluate the feasibility and effectiveness of preventive strategies in women who experience term GH or PE and have a 10-year cardiovascular event risk >10%. Furthermore the result will be submitted to national and international peer reviewed journals.

Duration

Duration of the study is 24 months

Remarks

HyRAS study was awarded with the poster prize at the Gynaecologescongres Zwolle May 2011.
HyRAS study was awarded with science prize of the Medical Centre Haaglanden.

Presentations

Hermes W, namens de HYRAS projectgroep: Classic Cardiovascular Risk Factors 2 Years after Pregnancy Complicated by Hypertensive Disease *at Term*. Society for Gynecological Investigations Miami. March 2011. Oral presentation.

Hermes W, namens de HYRAS projectgroep: Hypertension 6 Weeks and 2 Years after Term Pregnancies Complicated by Hypertensive Disorders. Society for Gynecological Investigations Miami. March 2011. Poster presentation.

Hermes W, namens de HYRAS projectgroep: Hypertension after Term Pregnancies Complicated by Hypertensive Disorders. Society for Maternal Fetal Medicine. Chicago. February 2011. Poster presentation.

PORTRET



Promovendus Drs. J. Labrie
Project leaders Dr. C.H. van der Vaart
ZonMw: 80-82310-98-08203
Nederlands Trial Register: NTR1248

Physiotherapy OR TvT Randomised Efficacy Trial

Achtergrond van het onderzoek:

De prevalentie van urine incontinentie bij lichamelijke inspanning is hoog. Ongeveer 20% van de volwassen vrouwen heeft deze zogenaamde stress incontinentie in meer of mindere mate. Naast de negatieve effecten op de kwaliteit van leven zijn er ook economische gevolgen. Per jaar wordt ongeveer € 120 miljoen aan incontinentiemateriaal uitgegeven. Specifieke bekkenbodemspieroefeningen door een daartoe speciaal getrainde fysiotherapeut wordt in het algemeen als eerste behandeling gezien. Ten opzichte van geen therapie is deze bewezen effectiever, maar slechts 15-25% zal compleet genezen en 25-50% van de vrouwen zal na fysiotherapie uiteindelijk toch een operatie ondergaan. Deze operatie, de TVT(O) procedure, is minimaal invasief met een genezingskans van 65-95%. Wel is er bij een operatie een wat verhoogde kans op nieuwe blaasklachten (6% ontwikkeld licht tot hinderlijke overactieve blaasklachten). Beide interventies zijn nooit head-to-head vergeleken en daaraan bestaat internationaal en nationaal grote behoefte binnen zowel de gynaecologie, urologie, huisartsgeneeskunde als de fysiotherapie.

Doel van het onderzoek:

Onderzoeken van de kosteneffectiviteit en klinische effectiviteit van de gespecialiseerde Bekkenbodemspieroefeningen in vergelijking met de TVT(O) operatie voor vrouwen met een matig tot ernstige urine incontinentie.

Onderzoeksopzet:

Multicentrisch gerandomiseerd onderzoek

Onderzoekspopulatie:

Wilsbekwame vrouwen tussen de 35-80 jaar met hinderlijke overwegend stress urine incontinentie die actief hulp zoeken.

Interventie (indien van toepassing):

Bekkenfysiotherapie door speciaal opgeleide en gecertificeerde bekkenfysiotherapeut TVT(O) operatie door ervaren gynaecoloog (> 20 procedures voorafgaande aan de studie). Bij de TVT(O) operatie wordt een kleine incisie onder de urethra geplaatst. Via deze incisie wordt een 1 cm brede polypropyleen tape ingebracht. Hetzij achter het os pubis langs, hetzij via het foramen obturator. De tape wordt spanningsloos (tension-free) gepositioneerd, waarna de wond en huidwondjes worden gesloten. Deze procedure neemt gemiddeld 15 minuten in beslag.

Primaire onderzoeksvariabelen/uitkomstmaten:

Primaire uitkomstmaat is complete genezing van de incontinentie.

Secundaire onderzoeksvariabelen/uitkomstmaten (indien van toepassing):

1. Kosteneffectiviteitanalyse
2. Subjectieve verbetering, oa. kwaliteit van leven
3. Ontwikkelen van een predictiemodel
4. Complicaties

Recruitment completed

PPROMEXIL



Promovendi David van der Ham/ Vie Curie
Jantien van der Heijden/ MMC Veldhoven
Projectleider: Dr. C. Willekes, AZM Maastricht
Clinical trials register ISRCTN 29313500
ZonMW 94507212

Inleiden van de bevalling versus afwachten bij vrouwen met vroegtijdig gebroken vliezen tussen 34 en 37 weken zwangerschapsduur

Problem:

Preterm prelabour rupture of the membranes (PPROM) is an important clinical problem and a dilemma for the obstetric gynaecologist. On one hand, awaiting spontaneous labour may lead to an increase in infectious disease for both mother and child, whereas on the other hand induction of labour leads to preterm birth with an increase in neonatal morbidity (e.g. respiratory distress syndrome (RDS)) and a possible rise in the number of instrumental deliveries.

Objective:

To determine the effectiveness and cost-effectiveness of induction of labour after PPRM between 34 and 37 weeks gestation compared to expectant monitoring.

Study Design:

Multicentre prospective randomised controlled trial.

Study Population:

Pregnant women with preterm premature rupture of the membranes at a gestational age from 34 + 0/7 weeks until 37 weeks.

Interventions:

We will compare induction of labour with expectant monitoring.

Outcome measures:

Primary outcome is neonatal infection. Secondary outcome measures are maternal morbidity (chorioamnionitis, puerperal sepsis) and neonatal disease, instrumental delivery rate, quality of life and costs.

Power/Data Analyses:

We anticipate that a reduction of neonatal infection from 7.5% to 2.5% will outweigh the differences of an increase in RDS and additional costs due to admission of the child due to prematurity. Under these assumptions, we will randomise 520 women (two groups of 260).

Economic Evaluation:

As we expect a reduction of infection in the intervention group, the economic analysis will be a cost-effectiveness analysis. Long term outcomes will be evaluated using modelling.

Trial end: September 2009, 525 inclusions.

Remarks:

A PPRMEXIL II study has been completed with 200 patients.

The authors have agreed with research from the Australian PPRMPT study that they will do an individual patient data meta-analysis.

Publications

van der Ham DP, van Melick MJ, Smits L, Nijhuis JG, Weiner CP, Beek JH, Mol BW, Willekes C. Methods for the diagnosis of rupture of the fetal membranes in equivocal cases: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2011 Apr 7. [Epub ahead of print]

van Teeffelen AS, van der Ham DP, Oei SG, Porath MM, Willekes C, Mol BW. The accuracy of clinical parameters in the prediction of perinatal pulmonary hypoplasia secondary to midtrimester prelabour rupture of fetal membranes: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2010 Jan;148(1):3-12. Epub . Review.

van de Laar R, van der Ham DP, Oei SG, Willekes C, Weiner CP, Mol BW. Accuracy of C-reactive protein determination in predicting chorioamnionitis and neonatal infection in pregnant women with premature rupture of membranes: a systematic review. *Eur J Obstet Gynecol Reprod Biol.* 2009 Dec;147(2):124-9. Epub 2009 Oct 12. Review.

van der Ham DP, van de Laar R, Mol BW, Willekes C. Use of C-reactive protein as a predictor of chorioamnionitis in preterm prelabour rupture of the membranes: a systematic review. *BJOG.* 2008 Jan;115(1):127; author reply 128. No abstract available.

van der Ham DP, Nijhuis JG, Mol BW, van Beek JJ, Opmeer BC, Bijlenga D, Groenewout M, Arabin B, Bloemenkamp KW, van Wijngaarden WJ, Wouters MG, Pernet PJ, Porath MM, Molkenboer JF, Derks JB, Kars MM, Scheepers HC, Weinans MJ, Woiski MD, Wildschut HI, Willekes C. Induction of labour versus expectant management in women with preterm prelabour rupture of membranes between 34 and 37 weeks (the PPROMEXIL-trial). *BMC Pregnancy Childbirth.* 2007 Jul 6;7:11.

Presentations

FNPS Meeting 2008 Oral presentation tijdens de FNPS meeting met als titel: Accuracy of C-reactive protein in predicting chorioamnionitis and neonatal sepsis in women with premature rupture of membranes: A systematic review

Presentatie Gynaecongres Presentatie tijdens het gynaecongres 4 juni 2010, Breda.

Posterpresentatie SMFM 2010, Chicago Posterpresentatie tijdens de SMFM meeting in Chicago, februari 2010

Posterpresentatie SGI 2010 , Orlando Posterpresentatie tijdens de SGI meeting in Orlando, maart 2010.

PROBAAT



Promovendus Drs. M. Jozwiak, Ikazia
Ziekenhuis Rotterdam

Project leader Dr. K. Bloemenkamp, LUMC
Leiden

Financiering: geen **Trialnummer:** NTR 1646

Background

Induction of labour is an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. Induction of labour is a common procedure: twenty-two percent of all deliveries were induced in the Netherlands in 2007. Compared to the spontaneous onset of labour, induction of labour is associated with prolonged labour, more instrumental deliveries and a higher rate of caesarean sections, especially when the cervix is unfavourable.

A recent Dutch survey showed a wide variety of methods being in use for induction of labour, intravaginal prostaglandin gel being used most frequently. A less frequently utilized method of ripening the uterine cervix is the transcervical Foley catheter. This inexpensive method is reported to have similar success-rates to induction of labour with intravaginal prostaglandins, and is associated with fewer abnormalities of contraction pattern and a lower caesarean section rate.

Objective

To assess in term pregnant women with an unfavourable cervix (Bishop score < 6) the effectiveness of induction of labour with a transcervical Foley catheter as compared to induction with prostaglandins.

Study design

Multicentre prospective randomised controlled trial. The study will be performed within a consortium of perinatal centres that are collaborating in several proposed studies.

Study population

Term pregnant women with an indication for induction of labour

Inclusion Criteria:

- Term pregnancy (≥ 37 weeks of pregnancy)
- Scheduled for induction of labour
- Vital singleton pregnancy
- Unfavourable cervix (Bishop score < 6)

Intervention

Induction of labour with a transcervical Foley catheter as opposed to intravaginal prostaglandins.

Main study parameters/endpoints

Caesarean section rate. Secondary outcomes will be maternal and neonatal morbidity and costs.

Analysis and sample size

Analysis will be by intention to treat. We need two groups of 406 women (812 women) to demonstrate a reduction in caesarean section rate from 25% to 17%.

Trial end: May 2010, 1200 randomisations

Presentations: Jozwiak et al. *PROBAAT study* Annual Meeting, San Fransico. February 2011. Oral presentation. Plenary session; abstract number 5.

Jozwiak et al; PROBAAT studie. Gynaecongres. November 2010.

SETI studie

Promovendus: Inge Custers, AMC Amsterdam

Projectleider: Prof. Dr. BW Mol AMC

Clinical trials register NTR824

Single Embryo Transfer or IUI

Behandeling onverklaarde subfertiliteit met lage kans op spontane zwangerschap. Een gerandomiseerd onderzoek om de werkzaamheid van IUI met ovariele hyperstimulatie en terugplaatsing van een enkel embryo na IVF te vergelijken.

Paren met onverklaarde onvruchtbaarheid en een lage kans op een spontane zwangerschap (< 30%) worden standaard behandeld met Intra Uterine Inseminatie (IUI) met milde ovariële hyperstimulatie. Deze behandeling resulteert in 10% tot 20% van de verkregen zwangerschappen tot dure en risicovolle meerlingzwangerschap. Meerlingzwangerschappen leiden veel vaker tot obstetrische en neonatale complicaties - zoals vroeggeboorte, groei retardatie en pre-eclampsie - dan eenlingzwangerschappen en zijn ook zeer kostbaar. Patiënten die na 6 IUI behandeling niet zwanger zijn geworden worden vervolgens standaard behandeld met In Vitro Fertilisatie (IVF) en het terug plaatsen van 2 embryo's.

Een alternatieve strategie, waarbij meerlingzwangerschappen voorkomen kunnen worden, is patiënten In Vitro Fertilisatie (IVF) met het terugplaatsing van één embryo (single embryo transfer of SET) aan te bieden, waarbij de rest van de verkregen embryo's wordt gecryopreserveerd (cryo-cycli). IVF is echter in vergelijking met IUI een voor de patiënt belastender behandeling.

De hypothese is dat één cyclus IVF-SET gevolgd door cryo-cycli gelijkwaardig is aan drie cycli IUI wat betreft de kans op een doorgaande zwangerschap en de aan de behandeling verbonden kosten bij patiënten met een kans op een spontane zwangerschap < 30%, terwijl de kans op een meerlingzwangerschap nagenoeg tot nul wordt gereduceerd.

Dit zal worden gestaafd in een gerandomiseerd onderzoek bij 100 paren met onverklaarde subfertiliteit en een lage kans op een spontane zwangerschap, die in aanmerking komen voor IUI. Daarbij is de primaire uitkomstmaat in eerste instantie een doorgaande zwangerschap, secundaire uitkomstmaten zijn meerlingzwangerschap, klinische zwangerschap, geboorte van een levend kind en zwangerschapscomplicaties. Daarnaast zal in deze gerandomiseerde studie ook de kosten-analyses en patiënten preferentie aan bod komen.

STan



Promovendus: Michelle Westerhuis/ UMC Utrecht

Jeroen Becker/ UMC Utrecht

Projectleider: Dr. A. Kwee, UMC Utrecht

Clinical trials register ISRCTN95732366 **ZonMw** 945-04-55

ST-analysis versus fetal blood sampling

Objective

Cardiotocography (CTG) is the method for fetal surveillance during labour worldwide. However, CTG alone shows many false positive results and without fetal blood sampling (FBS) it results in an increase in operative deliveries without an improvement of fetal outcome. FBS requires additional expertise, is invasive and often has to be repeated during labour. Two RCTs have shown that a combination of CTG and non-invasive ST-analysis (of the fetal ECG) reduces the rates of metabolic acidosis and instrumental delivery. However, in both RCTs FBS was still performed in both arms, and it is therefore still unknown if the observed results were indeed due to the ST-analysis or to the use of FBS in combination with ST-analysis. To quantify costs and effectiveness of non-invasive monitoring (CTG + ST-analysis) as compared to normal care (CTG + FBS), in order to judge whether the ST-analysis can replace FBS.

Study design

Multicentre randomised controlled trial in eight hospitals.

Study population

Women in labour (above 36 weeks of gestation) with an indication for CTG.

Intervention

Women will be randomised for fetal surveillance with CTG + FBS or CTG + ST-analysis.

Outcome measures

Primary outcome is the incidence of metabolic acidosis (defined as pH below 7.05 and BDecf above 12 mmol/l in the umbilical cord artery). Secondary outcome measures are: instrumental delivery rate, cost-effectiveness, neonatal outcome (Apgar score, admission to a neonatal ward) and cost-effectiveness of both monitoring strategies across hospitals.

Power/ data analysis:

The analysis will follow the intention to treat principle. The incidence of metabolic acidosis will be compared across both groups. Assuming a reduction of metabolic acidosis from 3.5 to 1.5 %, using a two sided test with an alpha of 0.05 and a beta of 0.80, in favour of CTG + ST-analysis, 2400 women have to be randomised (1200 per group).

Economic evaluation:

The economic evaluation is designed as cost-effectiveness analysis, i.e. the ratio of (I) incremental costs and (II) the reduced rate of metabolic acidosis, associated with the strategies is quantified.

Trial end:

July 2008, 5700 randomisations

Remarks Prize winning paper at the Society for Gynaecological investigations. Glasgow. 2009.

Peer-reviewed articles:

Becker JH, Westerhuis MEMH, Sterrenburg K et al. The value of fetal blood sampling in addition to ST-analysis of the fetal electrocardiogram: results from the Dutch STAN trial. *BJOG*. In press.

Vijgen SMC, Westerhuis MEMH, Opmeer BC et al. Cost-effectiveness of cardiotocography plus ST-analysis of the fetal electrocardiogram compared to cardiotocography only. *Acta Obstet Gynaecol Scandinavica*. In press.

Westerhuis MEMH, Visser GHA, Moons KGM, Zuithoff NPA, Mol BWJ, Kwee A. Letter to the editor to: Cardiotocography plus ST analysis of fetal electrocardiogram compared with cardiotocography only for intrapartum monitoring: a randomized controlled trial. *Obstet Gynecol* 2011; 117 (in press).

Westerhuis MEMH, Visser GHA, Moons KGM, et al. Cardiotocography Plus ST Analysis of Fetal Electrocardiogram Compared With Cardiotocography Only for Intrapartum Monitoring: A Randomized Controlled Trial. *Obstet Gynecol* 2010;115:1173-80.

Westerhuis MEMH, Strasser SM, Moons KGM, Mol BWJ, Visser GHA, Kwee A. Foetale bewaking intra partum: van stethoscoop naar ST-analyse van het ECG. *Ned Tijdschr Geneesk.* 2009;153:B259

Westerhuis MEMH, van Horen E, Kwee A, van der Tweel I, Visser G, Moons K. Inter- and intra-observer agreement of intrapartum ST analysis of the fetal electrocardiogram in women monitored by STAN. *BJOG* 2009;116:545-551.

Westerhuis MEMH, Moons KG, van Beek E, et al. A randomised clinical trial on cardiotocography plus fetal blood sampling versus cardiotocography plus ST-analysis of the fetal electrocardiogram (STAN) for intrapartum monitoring. *BMC Pregnancy Childbirth* 2007; 26: 7-13.

Westerhuis MEMH, Kwee A, Van Ginkel AA, Drogtop AP, Gyselaers JA, Visser GHA. Limitations of ST-analysis in clinical practice: three cases of intrapartum metabolic acidosis. *BJOG* 2007; 114: 1194-201.

Het Consortium Verloskundig Onderzoek. Evaluatieonderzoek in de Nederlandse verloskunde: uitvoering van 6 gerandomiseerde trials binnen een landelijk netwerk. *Ned Tijdschr Geneesk.* 2007; 151: 771-5.

Gyselaers W, Indrato R, Westerhuis MEMH, Visser GHA, Rosen K. STAN-recorded intrapartum loss of beat-to-beat variation associated with prolonged QT-interval: indicative for fetal hypocalcemia? *J Matern Fetal Neonatal Med* 2007; 20: 69-73.

Ayres-de-Campos D, Bernardes J, Kwee A, Westerhuis MEMH, Visser GHA. Computer quantification of short-term variability as an adjunct to fetal electrocardiographic monitoring. *BJOG* 2007; 114: 1445-6.

Other articles:

Westerhuis MEMH, Visser GHA, Kwee A. ST-analyse in Nederland: de STAN(d) van zaken. *Nederlands tijdschrift voor Obstetrie & Gynaecologie* 2010; 123:198-202.

Westerhuis MEMH, Kwee A. Intrapartum foetale bewaking: MBO of STAN? *Nederlands tijdschrift voor Obstetrie & Gynaecologie* 2006; 119: 33-34.

Presentations

Westerhuis MEMH. The Dutch STAN trial. Swedish conference on intrapartum fetal monitoring. 27 October 2010, Stockholm, Sweden. Oral presentation.

Westerhuis MEMH. De nederlandse STAN trial. STAN minisymposium Universitair Ziekenhuis Antwerpen, 28 september 2010, Antwerpen, Belgium. Oral presentation.

Westerhuis MEMH en Kwee A. De nederlandse STAN trial en secundaire analyses. BMA mini symposium, 16 september 2010, Utrecht, The Netherlands. Oral presentations.

Westerhuis MEMH. Intrapartum foetale bewaking. STAN versus CTG: een update. Refereeravond VU Medisch Centrum, april 2010, Amsterdam, The Netherlands. Oral presentation.

Westerhuis MEMH for the STAN study group. Intrapartum fetal monitoring: identification of cases with adverse neonatal outcome. SMFM annual meeting February 2010. Chicago, USA. Oral presentation.

Westerhuis MEMH for the STAN study group. Prediction of neonatal metabolic acidosis in women with a term singleton fetus in cephalic position. SMFM annual meeting February 2010. Chicago, USA. Poster presentation.

Becker JH for the STAN study group. The value of fetal blood sampling in addition to ST-analysis of the fetal electrocardiogram: results from the Dutch STAN trial. SMFM annual meeting February 2010. Chicago, USA. Poster presentation.

Vijgen SMC for the STAN study group. Cost-effectiveness of cardiotocography plus ST-analysis of the fetal electrocardiogram compared to cardiotocography only. SMFM annual meeting February 2010. Chicago, USA. Poster presentation.

Kwee A. De plaats van het MBO en navelstrengbloedgasen op de verloskamer. Bloedgassensymposium. Maart 2010, Utrecht, The Netherlands. Oral presentation.

Kwee A. Foetale Bewaking anno 2010. De STAN(d) van zaken. Siemens symposium Zuur-base diagnostiek rondom de geboorte. Mei 2010, Zeist, The Netherlands. Oral presentation.

Westerhuis MEMH for the STAN study group. Intrapartum fetal monitoring by ST-analysis of the fetal electrocardiogram versus cardiotocography: a Dutch randomised clinical trial. SGI annual meeting March 2009. Glasgow, Scotland. Oral presentation.

Kwee A, Westerhuis MEMH, Visser GHA. Eerste resultaten van de Nederlandse STAN-trial. Doelencongres 2009, Rotterdam, The Netherlands. Oral presentation.

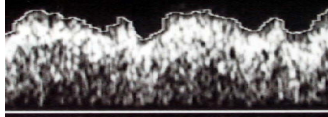
Kwee A. De Nederlandse STAN-trial. GEM-congres, maart 2009, Putten, The Netherlands. Oral presentation.

Kwee A. Uitkomsten STAN-trial. BMA gebruikersdag, september 2009, congres Oegstgeest, The Netherlands. Oral presentation.

Kwee A for the STAN study group. ST-analysis of the fetal ECG: Results from the Dutch RCT (invited lecture). October 2009, 9th World Congress Perinatology, Berlin, Germany. Oral presentation.

Kwee A for the STAN study group. Results of the Dutch STAN-trial (invited lecture). December 2009, French Annual Meeting Gynaecology, Paris, France. Oral presentation.

TRUFFLE



Trial of Umbilical and Fetal Flow in Europe (Truffle)
Projectleider: Dr. H. Wolf, AMC Amsterdam
Promovendus: Nico Mensinck
Clinical trials register ISRCTN volgt ZonMW 945-06-556

How to decide the best timing of delivery in preterm pregnancies complicated by intrauterine growth restriction

Background

Optimal management of severe early fetal growth restriction is one of the greatest challenges in Obstetrics. In case of abnormal fetal monitoring obstetricians are often uncertain when to deliver these babies and how to balance between the complications of extreme preterm delivery and the risks of prolonged intrauterine exposure to malnutrition, hypoxia and the risk of death. Prospective observational research by the study group and others has provided evidence that Doppler measurement of the fetal ductus venosus (DV) may be the best parameter to guide timing of delivery in these pregnancies. However this hypothesis needs further evidence.

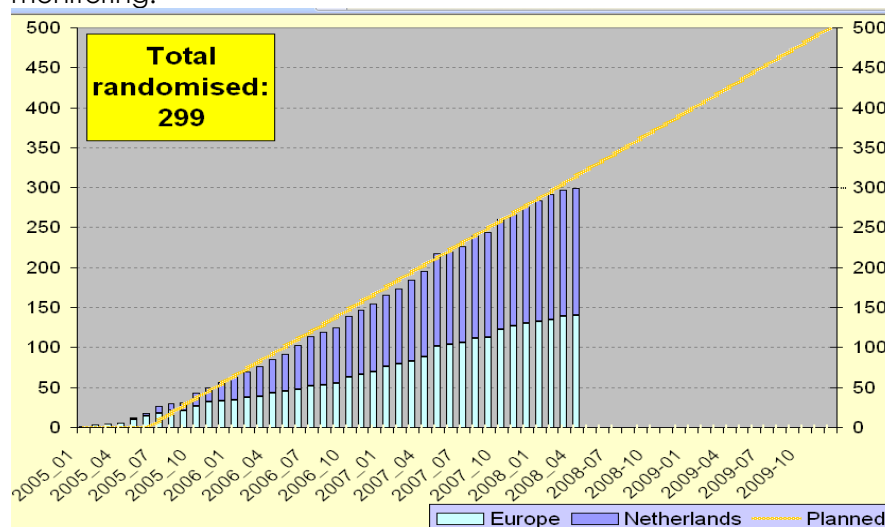
Objective

The objective of this multi-centre randomised protocol, approved by the Lancet, is to determine which technique results in optimal timing of delivery of early preterm growth restricted infants: DV measurement (two different cut-offs - 1. mild or 2.severe abnormality-will be tested) or traditional monitoring based on 3.cardiotocography (STV). Criteria for inclusion aim at selecting a group of early and severe growth restricted fetuses. Randomisation will assign fetuses to the three branches.

Outcome measures and analysis

The primary outcome is normal neurological outcome at 2 years corrected age, without minor or major sequelae, examined by Griffith's Mental Developmental Scale. Two years is the earliest age to evaluate the infant development. The hypothesis of the study is that among preterm growth-restricted infants, timing delivery when the fetal DV is just marginally or severely abnormal, i.e. before the onset of severe fetal hypoxemia, increases the rate of normal infant neurological outcome compared with timing of delivery based on severe changes in fetal heart short-term variation.

The study will determine if timing delivery based on changes of fetal hemodynamic modifications monitored by venous Doppler velocimetry, where they precede a non-reassuring fetal heart rate pattern, is more effective than using computerised fetal heart rate monitoring.



**Objective:**

To test the value of preoperatively performed urodynamics with regard to outcome of surgery for stress urinary incontinence (SUI) and to examine whether it is costeffective not to perform urodynamics preoperatively using the non-inferiority assumption.

Study design:

Multicentre, randomized controlled multidisciplinary trial.

Study population:

Women with symptomatic stress urinary incontinence in whom conservative measures failed and in whom surgical treatment is considered. Only those women in whom the urodynamic findings are discordant with the findings based on history, clinical examination and 48h voiding diary will be randomized.

Intervention:

Surgical therapy versus any other therapy (surgical therapy or conservative treatments) as based on individual findings.

Outcome measures:

Primary outcome: Non inferiority of the improvement of the UDI one year after treatment.
Secondary outcomes: Cure of incontinence as measured with voiding diary. Complications of surgery for stress incontinence in particular re-operation and overactive bladder symptoms of quality of life as measured by validated questionnaires.

Power / data analysis:

600 women will be included in the study, of whom 200 women will have discordant findings between history and urodynamics. Anticipating a 50% participation rate of women with discordant findings will be randomized to each group (51 per group). As based on the non-inferiority assumption, the mean improvement in UDI in both groups is expected to be 35 with standard deviation 10. A difference in mean improvement of 5 or less is considered non-inferior (power 80% using one-sided testing at 0.05).

Economic evaluation:

For each patient, utilization of health care services will be recorded prospectively, using Case Record Forms, including urodynamic testing, surgery for SUI, re-operations, medical treatment for detrusor instability, care for urinary incontinence, and care for urinary retention.

Time schedule: Start inclusion September 2008. Recruitment completed end 2010. Follow up 24 months.

Publications

Sanne AL van Leijsen, Kirsten B Kluivers, Ben Willem J Mol, Suzan R Broekhuis, Fred L Milani, C Huub van der Vaart, Jan-Paul WR Roovers, Marlies Y Bongers, Jan den Boon, Wilbert A Spaans, Jan Willem de Leeuw, Viviane Dietz, Jan H Kleinjan, Hans AM Brölmann, Eveline J Roos, Judith Schaafstra, John PFA Heesakkers and Mark E Vierhout. Protocol for the Value of Urodynamics prior to Stress Incontinence Surgery; a multicenter randomized controlled trial to assess the cost effectiveness of urodynamics in women with symptoms of stress urinary incontinence in whom surgical treatment is considered. *BMC Women's Health* 2009, 9:22

van Leijsen SA, Evert JS, Mol BW, Vierhout ME, Milani AL, Heesakkers JP, Kluivers KB. The correlation between clinical and urodynamic diagnosis in classifying the type of urinary incontinence in women. A Systematic review of the literature. *Neurourol Urodyn.* 2011 April; 30 (4): 495-502.

When outcome is in balance

Health Technology Assessment. ZonMW 945-04-558

Summary

Many clinical studies in obstetrics face a multidimensional outcome, resulting in complex decisions on the design, analysis and derivation of recommendations. A prototypical outcome problem is at the core of this HTA-study.

When problems arise during third trimester pregnancy (e.g. pre-eclampsia, suspected growth retardation) the obstetrician has to choose between a watchful waiting versus an active (induction of labour, caesarean sectio [CS]) strategy. Active policy: less risk of intrauterine death, more risk on prematurity, labour complications, disadvantages of a CS; watchful waiting involves the reverse. Probabilities of these events range from rare to universal, and the weights attached to these outcomes show a broad range.

We propose to compare head-to-head methodologies in use in so-called preference and utility measurement to arrive at a preferred method to measure and analyse these multidimensional outcomes. The primary comparison will be the 'attitude' method based in psychology, applying, for short rating scales and sophisticated analysis to cover personal effects and error, and the 'preference' method based in economics, with 2 branches: indirect trade-offs with an artificial calibration scale as in time-trade-off or WTP, or so-called direct discrete choice experimentation (DCE) choosing between 2 vignettes, as in conjoint analysis).

Project members

Prof. Dr. G.J. Bonsel, AMC Amsterdam

Dr. E. Birnie, AMC Amsterdam

Dr. B.W. Mol, MMC Veldhoven

Drs. D. Bijlenga, AMC Amsterdam

Time schedule

April 2005 to March 2008

Project completed

Publications

Eliciting willingness to pay in obstetrics: comparing a direct and an indirect valuation method for complex health outcomes. Bijlenga D, Bonsel GJ, Birnie E. Health Econ. 2010 Oct 22. [Epub ahead of print]

Feasibility, reliability, and validity of three health-state valuation methods using multiple-outcome vignettes on moderate-risk pregnancy at term. Bijlenga D, Birnie E, Bonsel GJ. Value Health. 2009 Jul-Aug;12(5):821-7.

When outcome is a balance: methods to measure combined utility for the choice between induction of labour and expectant management in mild risk pregnancy at term. Bijlenga D, Birnie E, Mol BW, Bonsel GJ. BMC Pregnancy Childbirth. 2007 Jul 4;7:10.

WOMB



Promovendus: Babette Prick, Erasmus MC

Project leaders Sanquin Blood Bank South West Region: DJ van Rhenen, Erasmus MC: JJ Duvekot

Subsidy: Landsteiner Foundation for Blood Transfusion Research

Clinical trials register : NTR335 | NCT0035023

Well being of Obstetric patients on Minimal Blood transfusions

De WOMB-studie, die al sinds 2004 liep in een aantal centra in de regio Rotterdam, werd in 2008 als studie van het onderzoeksconsortium opgestart. Inmiddels loopt de studie in 37 centra door heel Nederland. In een populatie van 400 vrouwen wordt onderzocht welke invloed wel of geen bloedtransfusie na de bevalling heeft op hun kwaliteit van leven. Sinds september 2008 worden er zo'n 6 patiënten per maand geïncludeerd.

Objective

Postpartum haemorrhage (PPH) is one of the top five causes of maternal mortality in developed and developing countries. The most important treatment of PPH is red blood cell (RBC) transfusion. The decision whether to prescribe RBC transfusion is mostly based on postpartum haemoglobin (Hb) values. RBC transfusion should be aimed to reduce morbidity and especially to improve Health Related Quality of Life (HRQoL). The goal of the WOMB study is to assess the effect of RBC transfusion on HRQoL and to confirm the role of HRQoL in deciding whether RBC transfusion is necessary.

Study design

Multicenter prospective randomised controlled trial. The study started in May 2004 and is ongoing in 37 hospitals in the Netherlands, which are collaborating in several trials.

Study population

Women with PPH or a decrease in Hb, 12 to 24 hours after delivery or caesarean section. The sample size will be 500 patients (where 250 patients receive a RBC transfusion and 250 patients don't) after vaginal or CS delivery.

Inclusion criteria:

- Blood loss during delivery = at least 1000 mL and/or a peripartum decrease in Hb of at least 1.2 mmol/L
- Hb level of 3.0 - 4.9 mmol/L, 12 to 24 hours after a vaginal delivery or caesarean section
- Women older than 18 years of age
- Good working knowledge of the Dutch language

Intervention: Patients will be randomised for a RBC transfusion or no transfusion.

Outcome measures: Primary outcome in this study is fatigue measured with the MFI questionnaire. The total follow-up period is 6 weeks. HRQoL will be measured at T=0 (12-24 hours postpartum) 3 days, 1, 3 and 6 weeks postpartum. At T=0 and 6 weeks postpartum Hb value will be measured as well as a screening on irregular antibodies. For the patients who receive a RBC transfusion, the effect of the RBC transfusion will be measured with the Hb value, Hct, platelet and leukocyte count, and the temperature of the patient before and after the RBC transfusion.

Trial end February 2011, 500 randomisations

Publications: Prick BW, Steegers EA, Jansen AJ, Hop WC, Essink-Bot ML, Peters NC, Uyl-de Groot CA, Papatsonis DN, Akerboom BM, Metz GC, Bremer HA, van Loon AJ, Stigter RH, van der Post JA, van Alphen M, Porath M, Rijnders RJ, Spaanderman ME, Schippers DH, Bloemenkamp KW, Boers KE, Scheepers HC, Roumen FJ, Kwee A, Schuitemaker NW, Mol BW, van Rhenen DJ, Duvekot JJ. Well being of Obstetric patients on Minimal Blood transfusions (WOMB trial). BMC Pregnancy Childbirth. 2010 ;10:83.

Lopende studies

ALLO



Promovendus Drs. J. Kaandorp, UMC Utrecht

Project leaders Dr. J. Derks, gynecologist, UMC Utrecht, Dr. M.J.L.N. Benders, neonatologist, UMC Utrecht

ZonMw 80-82305-98-09009

Nederlands Trial Register: NTR1383 **ClinicalTrials.gov,**

Protocol registration System: NCT00189007

Objective

Hypoxic-ischaemic encephalopathy is associated with development of cerebral palsy and cognitive disability later in life, and is therefore one of the fundamental problems in perinatal medicine. The xanthine-oxidase inhibitor allopurinol (ALLO) reduces the production of free radical formation, thereby limiting the amount of hypoxia-reperfusion damage. Animal and human studies suggest that administration of ALLO immediately prior to delivery in the case of suspected intra-uterine asphyxia might reduce hypoxic-ischaemic encephalopathy. In the present proposal, we aim to answer whether antenatal allopurinol administration does reduce hypoxic-ischaemic encephalopathy in neonates exposed to intra-uterine asphyxia.

Study design

Randomized double blind placebo controlled multicenter study

Study population

Women at term in whom the fetus is suspected of intra-uterine asphyxia

Intervention

Allopurinol or placebo administration antenatally to the mother.

Outcome measures

Primary outcome measures are the amount of S100B (a marker for brain tissue damage) and the severity of oxidative stress (measured by isoprostane, neuroprostane, non protein bound iron and hypoxanthine), both measured in umbilical cord blood. Secondary outcome measures are neonatal mortality, serious composite neonatal morbidity and long-term neurological outcome. Furthermore pharmacokinetics and pharmacodynamics will be investigated.

Power/data analysis

We expect an inclusion of 220 patients (110 per group) to be feasible in an inclusion period of two years. Given a suspected mean value of S100B of 1.05 ug/L (SD 0.37 ug/L) in the placebo group this trial has a power of 90% (alpha 0.05) to detect a mean value of S100B of 0.89 ug/L (SD 0.37 ug/L) in the 'allopurinol-treated' group (z-test 2-sided). Analysis will be by intention to treat and it allows for one interim analysis.

Economic evaluation

As the costs of ALLO and its administration are relatively low, a small treatment effect will already make the intervention cost-effective. We will perform economic modelling, in which we assess at what prevalence of encephalopathy administration of ALLO is cost-effective.

Time schedule 24 months

We plan to have 220 inclusions. Anticipated study end end 2011

Publication:

Kaandorp JJ, Benders MJ, Rademaker CM, Torrance HL, Oudijk MA, de Haan TR, Bloemenkamp KW, Rijken M, van Pampus MG, Bos AF, Porath MM, Oetomo SB, Willekes C, Gavilanes AW, Wouters MG, van Elburg RM, Huisjes AJ, Bakker SC, van Meir CA, von Lindern J, Boon J, de Boer IP, Rijnders RJ, Jacobs CJ, Uiterwaal CS, Mol BW, Visser GH, van Bel F, Derks JB. Antenatal allopurinol for reduction of birth asphyxia induced brain damage (ALLO-Trial); a randomized double blind placebo controlled multicenter study. BMC Pregnancy Childbirth. 2010 Feb 18;10:8.

ASB



Promovendus Drs. B. Kazemier

Project leader Prof. dr. C. de Groot, Gynaecologist,
VUMC Amsterdam

ZonMw

Nederlands Trial Register:

Objective

In the ASB-screen study, women with a healthy singleton pregnancy will be screened for asymptomatic bacteriuria. In the ASB-treat study we evaluate whether nitrofurantoin treatment for women with ASB is effective in reducing the risk of preterm delivery and/or pyelonephritis (primary outcome) and bad neonatal outcome (secondary outcome). In addition, we will assess whether it is cost-effective to screen and treat for ASB.

Study design

ASB-screen: Multicenter observational cohort study

ASB-treat: Multicenter double blind randomized clinical trial

Study population

Women with a singleton pregnancy and asymptomatic bacteriuria will be included. 4.400 women will be screened for the presence of ASB in the screen study, 500 are expected to be screen positive, in order to include 220 women in the randomized clinical trial.

Intervention

Nitrofurantoin 2x100 mg/day or placebo for 5 consecutive days.

Power analysis

Among women positive for ASB, we anticipate the occurrence of the primary outcome (delivery before 34 weeks and/or pyelonephritis) to be 10% in the treatment group and 25% in the no treatment group. ASB results often in an UTI (25-50% and these women are more prone to shock and respiratory distress syndrome). If ASB is not treated, 20% of pregnancies will be complicated by pyelonephritis compared to 2% of pregnancies without bacteriuria. Treatment of ASB results in a decrease of pyelonephritis (OR 0.24; 95%-CI 0.19-0.32, NNT 7) compared to women who were not treated. Using a two sided test with an alpha 0.05 and a beta of 0.8, 220 women with bacteriuria (110 per arm) are needed in the study. Anticipating a 5% prevalence of asymptomatic bacteriuria, we need to screen 4.400 women.

Economic evaluation

The study design will enable us to compare the costs and effects of the following strategies:

1. no screening for asymptomatic bacteriuria
2. screening for asymptomatic bacteriuria, and treatment of women with asymptomatic bacteriuria.

For each of these strategies, we will calculate the costs as well as the effects in terms of maternal urinary tract infection and bad neonatal outcome (mortality and severe morbidity, see above).

Time schedule

We will need a run-in period of six months for the study set up, and 12 months for inclusion. After inclusion of the last patient, 30 months (6 months pregnancy and 24 months for evaluating the child at age 2) are needed for follow-up data collection and report of results.

Subsidy

ZonMW – www.ZonMw.nl

APOSTEL I



Promovendi Drs. J.Y. Vis, AMC, Drs. F. Wilms
Project leaders Dr. M. Oudijk, gynecologist, UMCU,
Dr. B.W. Mol, gynecologist, AMC
ZonMw 80-82310-98-09056
Nederlands Trial Register: NTR1857

Objective To assess whether testing for fibronectin is a cost-effective strategy that prevents unnecessary treatment in women with threatened preterm labour.

Study design Multicenter randomized clinical diagnostic trial embedded in a cohort study. All patients will be tested for fibronectin and cervical length at admission. Patients with a positive fibronectin test or a cervical length below 10 mm will be treated with tocolysis. Those with negative fibronectin result and a cervical length between 10 – 30 mm will be randomised to tocolysis with nifedepin or to placebo. Patients with both a negative fibronectin test and a cervical length more than 30 mm will not be treated with tocolysis. The total cohort will be followed.

Study population Patients between 24 and 34 weeks of gestation associated with preterm labour will be invited to participate in the study.

Intervention Patients with a negative fibronectin test and a cervical length between 10 – 30 mm will be invited to participate in a randomized clinical trial of tocolysis or no additional treatment. Active treatment will be performed with the calcium entry blocker nifedipin. Active drug and placebo will be administered at the same volume and rate.

Outcome measures The primary outcome measure is number of days to delivery truncated at 7 days after study entry.

Secondary endpoints are, neonatal mortality, neonatal morbidity, maternal morbidity (side effects of tocolysis), costs, and health related quality of life.

Power/data analysis We propose a non-inferiority effectiveness trial. Based on our pilot study, we anticipate the probability on preterm birth within 7 days in the group of patients with a negative fibronectin test and a cervical length > 10 mm to be 5%. We need 220 patients (110 per arm) to assure with 80% power that the upper limit of the 95% one-sided CI for the difference in the proportion of preterm deliveries < 7 days will be within a prespecified non-inferiority boundary of 7.5%. The results of the randomised clinical trial will be analysed according to the intention to treat principle.

Economic evaluation The trial results will be combined with data from the prognostic cohort in a model. The average costs and effects of test with fibronectin strategy will be compared using the “treat all” strategy as the reference. Strategies with cervical length measurements will also be assessed. Long term outcomes will be evaluated using modelling.

Time schedule Start in 2009, duration 3 years.

Peer-reviewed articles Vis JY, Wilms FF, Oudijk MA, Porath MM, Scheepers HC, et al. Cost-effectiveness of fibronectin testing in a triage in women with threatened preterm labor: alleviation of pregnancy outcome by suspending tocolysis in early labor (APOSTEL-I trial). *BMC Pregnancy Childbirth*. 2009;9:38.

Why were the results of randomized trials on the clinical utility of fetal fibronectin negative? A systematic review of their study designs. Vis JY, Wilms FF, Oudijk MA, Bossuyt PM, van der Post JA, Grobman WA, Mol BW. *Am J Perinatol*. 2011 Feb;28(2):145-50. Epub 2010 Aug 12. Review.

Relationship between the time interval from antenatal corticosteroid administration until preterm birth and the occurrence of respiratory morbidity. Wilms FF, Vis JY, Pattinaja DA, Kuin RA, Stam MC, Reuvers JM, Mol BW. *Am J Obstet Gynecol*. 2011 Mar 26. [Epub ahead of print]

Time to Delivery after the First Course of Antenatal Corticosteroids: A Cohort Study. Vis JY, Wilms FF, Kuin RA, Reuvers JM, Stam MC, Pattinaja DA, Mol BW. *Am J Perinatol*. 2011 Jun 22. [Epub ahead of print]

APOSTEL III



Promovendus Drs. K. Heida
Project leaders Dr. M. Oudijk, gynecologist, UMCU,
Dr. B.W. Mol, gynecologist, AMC
Nederlands Trial Register: NTR 2947
Not funded

Assessment of Perinatal Outcome by use of Specific Tocolytics in Early Labour.
Subtitle: Nifedipine versus Atosiban in the treatment of threatened preterm labour.

Objective

Preterm labour is one of the most important obstetric problems throughout the Western world and occurs in approximately 10% of all deliveries. Preterm birth is the leading cause of perinatal mortality (70%) and accounts for 40% of severe neurological morbidity. Tocolysis for a period of two days is crucial in the treatment of threatened preterm labour, in order to allow for corticosteroids to exert their optimal effect on fetal lung development. The optimal tocolytic drug however, is subject to controversy. We hypothesize that Nifedipine as compared to Atosiban will result in an improved neonatal outcome.

Study design

Multicenter randomized controlled trial.

Study population

500 pregnant women with threatened preterm labour between 25 and 34 weeks gestational age.

Intervention

Nifedipine (dosage: 4 dd 20 mg orally for 48 hours) versus Atosiban (dosage: bolus injection of 6,75 mg i.v. in 1 minute, followed by 18 mg/hour for 3 hours followed by a maintenance dosage of 6 mg/hour for 45 hours) for 48 hours.

Outcome measures

The primary outcome of the study will be a composite for poor neonatal outcome. This outcome will include bronchopulmonary dysplasia (BPD), periventricular leucomalacia >grade 1, intracerebral haemorrhage >grade 2, necrotising enterocolitis >stage 1, proven sepsis and in-hospital death. Secondary outcomes will be time to delivery, gestational age at delivery, number of days on ventilation support, in NICU and total days of the baby alive outside the hospital counted from a gestational age of 37 weeks and maternal side effects.

Power/data analysis

The analysis will be by intention to treat. Adverse neonatal outcome will be tested for a difference of 10%. A difference in reduction of the composite poor neonatal outcome from 25% to 15%, with a beta of 0.2 and alpha of 0.05 can be detected if 500 patients are recruited (250 in each arm).

Economic evaluation

We will perform an economic analysis alongside the study, in which we will calculate the cost per prevented case of poor neonatal outcome. In case of no difference in primary outcome, we will calculate the number needed to treat with Atosiban to prevent a serious adverse drug reaction with Nifedipine.

Time schedule

Total 36 months.

BIG CHANGE

Promovendus Drs. S. Luitjes
Project leaders Dr.M.W. van Tulder, EMGO Institute
VU, dr. R.P.G.M. Hermens, UMC Nijmegen, dr.
M.G.A.J. Wouters, VUmc
ZonMw: 170883003
Nederlands Trial Register: 1387

BOS supported implementation of guidelines on clinical hypertension and its management in gestation

Objective

Hypertension is a common complication of pregnancy. Seventeen percent of the clinical pregnancies are complicated by hypertension and 2% by preeclampsia. Severe hypertension and preeclampsia (hypertension and proteinuria) poses an increased risk for mortality and morbidity to both the mother and the fetus. The Dutch trends in maternal morbidity due to severe hypertension and preeclampsia are currently a reason for great concern. It is thought that a high degree of these maternal complications results from suboptimal or insufficient treatment. A recent study showed that in 96% of the cases of maternal death several factors of substandard care were present. In 85% of the cases, these factors were classified as insufficient treatment of hypertension. Therefore, the management of hypertension is an important part of the care of pregnant women for which improvement is necessary. The NVOG has developed evidence-based guidelines on the management of hypertension in pregnancy and chronic hypertension. However, it seems likely that these guidelines are not implemented yet. In order to reduce maternal complications, an implementation strategy to improve adherence to the guidelines on hypertension in pregnancy is necessary. The main objective of this study is to assess the cost-effectiveness of an innovative implementation strategy of the NVOG guidelines on hypertension including a computerised decision support system (BOS) and professional audit and feedback compared to a common strategy of professional audit and feedback.

Study design

A cluster randomized controlled trial with an economic evaluation alongside will be performed.

Outcome measures

The primary outcome measures for the evaluation of the effectiveness of both strategies is a combined rate of major maternal complications (maternal death, organ specific complications of hypertension, HELPP syndrome, placental abruption). Secondary outcome measures for effectiveness are guidelines' adherence rates, fetal death rates, Caesarean delivery rates, rates of neonatal mortality and morbidity.

Publications Study protocol: Cost effectiveness of two strategies to implement the NVOG guidelines on hypertension in pregnancy: An innovative strategy including a computerised decision support system compared to a common strategy of professional audit and feedback, a randomized controlled trial. Luitjes SH, Wouters MG, Franx A, Scheepers HC, Coupé VM, Wollersheim H, Steegers EA, Heringa MP, Hermens RP, van Tulder MW. *Implement Sci.* 2010 Sep 6;5:68.

**Control of Hypertension In Pregnancy Study****Objective**

Women with non-severe non-proteinuric pre-existing hypertension (1% of deliveries) or gestational hypertension remote from term (2-3%) represent a high-risk group from both maternal and perinatal perspectives. Based on our meta-analyses of RCTs, arguments can be made both for and against less tight control of BP (allowing for higher BP levels). Less tight control may decrease the risk of small for gestational age (SGA) infants, but may also increase the risk of (transient) severe maternal hypertension, antenatal hospitalisation, and proteinuria at delivery.

Study design

International multicentre RCT that will recruit over 4 years.

Study population

1,028 women (514/group) from 50 tertiary and community centres.

Intervention

Eligible women will be randomised centrally to either less tight control (aiming for dBP of 100mmHg) or tight control (aiming for dBP of 85mmHg) of their hypertension. Randomisation will be stratified by centre and type of hypertension (pre-existing or gestational). In the less tight control group, if dBP is = 105mmHg, then antihypertensive medication must be started or increased in dose. In the tight control group, if dBP is = 80mmHg, then antihypertensive medication must be decreased in dose or discontinued.

Outcome measures

Primary: Pregnancy loss (miscarriage, pregnancy termination, stillbirth, or neonatal death) or NICU admission for >48hr in the first 28 days of life or prior to primary hospital discharge, whichever is later. Secondary: One/more serious maternal complication(s) until six weeks postpartum

Power/data analysis

Reduction in pregnancy loss or high level neonatal care for > 48hr from 33% to 25%: the final sample size of 514/group was based on a two-tailed alpha of 0.05, power of 80%, rates of the primary outcome of 33% in the tight control group and 25% in the less tight control group (after a crossover of 10% of patients to the alternate treatment), and two interim analyses (after 1/3 and 2/3 of patients have been evaluated for the primary outcome). The sample size was inflated by 1% to account for loss to follow-up. This sample size will give us 78% power (alpha of 0.05, two-sided) to find an increase of 5% in adverse maternal outcome in the less tight control group. This is based on a risk of serious maternal complications of 7% in the tight control group, based on inclusion of additional maternal outcomes from the PIERS (Pre-eclampsia Integrated Estimate of Risk Study) project.

Time schedule

Recruitment during a 4 year period from April 2009.

ECV Implementatie



Promovendi Drs. F. Vlemmix, drs. A. Rosman, AMC
Project leaders Dr. M. Kok, dr. B.W. Mol, AMC
ZonMw 170993006
Nederlands Trial Register: niet van toepassing

Objective

Breech presentation occurs in 3 – 4 % of all term pregnancies. External cephalic version (ECV) is an intervention to prevent breech position at delivery and is therefore advised in guidelines for gynecologists and midwives. The implementation of external cephalic version is at maximum 70%, but probably less, and success rates of ECV are only 40%. The aim of the present study is to identify both impeding as well as facilitating factors and to develop and evaluate an implementation strategy based on proper counseling of pregnant women and their care providers.

Study design

During the first phase of the project we will identify both facilitating as well as impeding factors. Subsequently we will identify an implementation strategy focused on counseling of pregnant women with a child in breech position and counseling of their health care providers. In the third phase of the project we will evaluate in a randomized clinical trial the effectiveness of the developed strategy. The study will be performed in 32 of the 100 Dutch hospitals.

Intervention

External cephalic version in breech position

Outcome measures

Primary: the number of patients that undergo an external cephalic version procedure.
Secondary: we will look at the number of babies in cephalic position at delivery.
Complications as a consequence of external cephalic version and the number of Caesarean sections as well as perinatal condition of mother and child. We will also assess the cost effectiveness of implementation strategies.

Time schedule

- Assessment of barriers and facilitators: 12 months
- Development of the strategies: 6 months
- Randomised clinical trial: 12 months
- Evaluation and report: 6 months

Publications Vlemmix F, Rosman AN, Fleuren MA, Rijnders ME, Beuckens A, Haak MC et al. Implementation of the external cephalic version in breech delivery. Dutch national implementation study of external cephalic version. *BMC Pregnancy Childbirth* 2010; 10:20.

Presentations

Why do patients opt for or refuse external cephalic version in breech position and how care providers can help to make a supported decision. A.N. Rosman, F.Vlemmix, A. Beuckens, M.E. Rijnders, A.H. Fleuren, B.O. Opmeer, B.W.J. Mol, M. van Zwieten, M. Kok International Shared Decision Making conference, Maastricht 2011. Poster presentation:

Factors associated with adherence to the guideline recommendation for external cephalic version in women with a breech presentation at term. F.Vlemmix, A.N. Rosman, A. Beuckens, M.E. Rijnders, B.O. Opmeer, B.W.J. Mol, M. Kok, M.A.H. Fleuren. International Shared Decision Making conference, Maastricht 2011. Oral presentation.

Contraindications of external cephalic version in breech position: a systematic review: Rosman A.N.; Guijt A; Vlemmix F; Mol B.W.J.; Kok M. ICM (International Congress of Midwives) Durban 2011. Oral presentation

ESEP



Promovendus Drs. F. Mol
Project leaders Dr. P. Hajenius, dr. B.W. Mol
ZonMw: Agiko stipendium grant 920-03-328,
Clinical fellow grant 40-00703-97-05-154
Nederlands Trial Register: NTR115

European Surgery Ectopic Pregnancy

Randomised controlled trial of salpingo(s)tomy versus salpingectomy for tubal pregnancy; the impact on future fertility

Background The incidence of tubal pregnancy is approximately 1-2 % of all pregnancies. Whether surgical treatment should be performed conservatively or radically in patients who want to preserve their reproductive capacity is subject to debate.

Objective The conservative approach, salpingo(s)tomy, preserves the tube, but bears the risk of persistent trophoblast and of repeat tubal pregnancy. The radical approach, salpingectomy, bears no risk of persistent trophoblast and limits the risk of repeat tubal pregnancy, but leaves only one tube for reproductive capacity. Our objective is whether the potential advantage of salpingo(s)tomy, i.e. a better fertility prognosis as compared to salpingectomy, outweighs the potential disadvantages of this treatment, i.e. persistent trophoblast and an increased risk for ectopic pregnancy.

Study-design International multi centre randomised controlled trial in a Dutch-Swedish-British-American collaboration.

Population All hemodynamically stable patients with a presumptive diagnosis of tubal pregnancy, who are scheduled for surgical treatment, will be eligible for the trial. Excluded are patients pregnant after IVFET or ICSI and/or with known tubal pathology. At surgery, that can either be performed laparoscopically or by laparotomy, the presence of a tubal pregnancy must be confirmed. Only patients with a tubal pregnancy that allows both interventions, and a contra lateral tube that would allow spontaneous conception in case of salpingectomy, are being included. Randomisation will be performed during surgery with an internet randomisation program.

Intervention and follow-up Salpingo(s)tomy and salpingectomy are performed following standard procedures used in the residential hospitals. For a period of 36 months, every six months, starting from the date of the operation, the patient will be contacted to assess her fertility status by means of a questionnaire.

Outcome measures and analysis The primary outcome measure is the occurrence of spontaneous vital intra uterine pregnancy. Secondary outcome measures are persistent trophoblast and repeat ectopic pregnancy.

Time schedule Start in 2004, anticipated study end mid 2011

Salpingotomy or salpingectomy in tubal ectopic pregnancy: what do women prefer? van Mello NM, Mol F, Opmeer BC, de Bekker-Grob EW, Essink-Bot ML, Ankum WM, Mol BW, van der Veen F, Hajenius PJ. *Reprod Biomed Online*. 2010 Nov;21(5):687-93. Epub 2010 Jun 30.

The ESEP study: salpingostomy versus salpingectomy for tubal ectopic pregnancy; the impact on future fertility: a randomised controlled trial. Mol F, Strandell A, Jurkovic D, Yalcinkaya T, Verhoeve HR, Koks CA, van der Linden PJ, Graziosi GC, Thurkow AL, Hoek A, Hogström L, Klinte I, Nilsson K, van Mello NM, Ankum WM, van der Veen F, Mol BW, Hajenius PJ; European Surgery in Ectopic Pregnancy study group. *BMC Womens Health*. 2008 Jun 26;8:11.

FLUXIM



Promovendus Drs. M. Woiski, UMC St. Radboud
Project leaders Dr. R. Hermens, UMC St. Radboud,
Dr. H.C.J. Scheepers, Maastricht UMC
ZonMw 80-82315-98-09003
Nederlands Trial Register: niet van toepassing

Objective The most important cause of maternal morbidity in the Netherlands is Hemorrhagia post partum (HPP), with an incidence of 5% containing 10.000 women in the Netherlands a year. Introduction of an evidence-based guideline about HPP by the Dutch society of Obstetrics and Gynaecology (NVOG) and the course Management of Obstetrics Emergencies and Trauma (MOET course) did not lead to a reduction in HPP. This implies the possibility of an incomplete implementation of both the NVOG guideline and MOET-instructions.

Study design To evaluate the implementation of the guideline and MOET instruction in the current care, measurement of the actual care will be performed in a representative sample of 20 hospitals. This will be done by prospective observation of the third stage of labor of 400 women with a high risk of HPP by using quality indicators extracted from the NVOG guideline and MOET instructions.

Barriers and facilitators for the guideline adherence will be analyzed by performance of semi structured interviews with 30 professionals and 10 patients and a questionnaire among all Dutch gynaecologists and midwives.

In a feasibility study in 4 hospitals a tailor made strategy to implement the NVOG guideline and MOET instructions, based on the outcome of the two studies above, will be tested. In this feasibility study an effect-, process- and cost-evaluation will be performed

Study population All women with a higher risk of HPP.

Outcome measures Adherence to the quality indicators regarding the process, structure and outcome of care around childbirth (e.g. incidence of HPP). Process-measures regarding the degree of making use of and experience with the various parts of the implementation strategy among professionals. Costs of the different parts of the implementation strategy

Power/data analysis With an estimation of adherence to the guidelines of 50%, a precision of estimation of guideline adherence of 7.5% and an icc of 0.20, 320 women have to be included in the actual care study

Economic evaluation Cost-evaluation of the different parts of the implementation strategy will be made

Time schedule 36 months, 6 months of preparation, 30 months inclusion, interviews, feasibility study and analysis and report

Publications Woiski MD, Scheepers HCJ, Lotgering FK, Grol RP, Hermens RPGM; *Development of guideline-based quality indicators for post partum hemorrhage (PPH) to improve quality of care* Otolaryngology-Head and Neck Surgery : Volume 143 Number 1S1, July 2010

Woiski MD, Schepers HCJ, Hermens RPMG for the Fluxim study group.: *Hoe verbeteren we de kwaliteit van zorg omtrent haemorrhagia post partum in Nederland.* (Ingezonden brief). NTOG, vol 123, feb 2010

Woiski MD, Hermens RPMG, Middeldorp JM, Kremer JA, Marcus MA, Wouters MGAJ, Grol RP, Lotgering FK, Scheepers HCJ *Haemorrhagia post partum; an implementation study on the evidence-based guideline of the Dutch Society of Obstetrics and Gynaecology (NVOG) and the MOET (Managing Obstetric Emergencies and Trauma-course) instructions; the Fluxim study.* BMC Pregnancy Childbirth 2010 Jan, 10:15.

Presentations: Woiski MD: Development of guideline-based quality indicators for post partum hemorrhage (PPH) to improve quality of care. Guidelines International Network (GIN) Conference 2010, August 2010, Chicago. Oral presentation

GLucoMOMS



Promovendus Drs. D. van Munster

Project leaders Dr. I.M. Evers, gynaecologist, Meander MC; Dr. H.W. de Valk, diabetologist, UMCU, Prof. dr. A. Franx, gynaecologist, UMCU, Prof. dr. B.W. Mol, gynaecologist, AMC

ZonMw 80-82310-97-11157

Nederlands Trial Register:

Effectiveness of continuous glucose monitoring during pregnancy in women with type 1 and type 2 diabetes.

Objective

In this study, we aim to assess the effectiveness, costs and cost-effectiveness of the use of the Continuous Glucose Monitoring System to optimize glycemic control during diabetic pregnancies and reduce macrosomia, relative to standard control methods.

Study design

Multicenter open label randomized clinical trial with a decision and cost-effectiveness study.

Study population

Pregnant women with type 1 and 2 diabetes.

Inclusion Criteria

Pregnant women with pre-existing diabetes (type 1 or type 2) before 16 weeks GA, on intensive insulin treatment regimen or use of insulinpump.

Exclusion Criteria

Severe medical or psychological comorbidity, multiple pregnancies

Intervention

Consenting women will be randomly allocated to either additional use of CGMS or usual care. All women will determine their glycemic control by self-monitoring of blood glucose levels and HbA1c. In addition, women allocated to CGMS will use CGMS every month and adjust their insulin regimen based on their CGMS profile.

Outcome measures of the RCT

Primary outcome of the RCT will be macrosomia rate, defined as a birth weight above the 90th centile. Secondary outcomes will be birth weight, composite neonatal morbidity, maternal outcome and costs. The analyses will be according to the intention to treat principle.

Sample size calculation

We anticipate that a reduction of macrosomia from 45% to 30% will outweigh the costs of the additional use of the CGMS. Under these assumptions, we need to randomize 300 women (two groups of 150).

Economic evaluation

As we expect a reduction of macrosomia but an increased use of resources in the intervention group, the economic analysis will be a cost-effectiveness analysis, with the costs per prevented case of macrosomia as the primary outcome measure, and a cost-benefit-analysis based on modeling.

Time schedule

Total study time 24 months.

HYPITAT II



Promovendus Drs. J. Langenveld, Maastricht UMC

Project leaders

Dr. M. Porath, gynecologist, MMC Veldhoven

Dr. M.G. van Pampus, gynecologist, UMC Groningen.

Subsidy: ZonMW 80-82310-971-017

Trial nummer: NTR1766

Objective At present, there is no evidence on the effectiveness and efficiency of induction of labour in women with pregnancy induced hypertension or mild preeclampsia with a gestational age of 34-37 weeks of pregnancy, as compared to expectant management under regular monitoring.

Study design

Multicentre randomized controlled clinical trial

Study population

Pregnancy induced hypertension or preeclampsia at a gestational age between 34+0 and 37+0 weeks

Intervention

Induction of labour, if necessary preceded by artificial ripening versus expectant monitoring. In case of a contraindication for vaginal delivery, for example a breech presentation, a Caesarean section will be performed if this is agreed in by the patient and her physician.

Outcome measures

Primary outcome measure

The maternal primary outcome measure will be a composite endpoint of maternal mortality, maternal complications (eclampsia, HELLP syndrome, pulmonary edema) and progression to severe pre-eclampsia. The neonatal primary outcome measure will be respiratory distress syndrome (RDS), which can be complicated by fetal mortality in rare cases.

Secondary outcome measures

Secondary maternal outcomes will be caesarean section rate, instrumental vaginal delivery rate, maternal quality of life and quality of recovery and costs. Secondary neonatal outcome will be neonatal morbidity defined as neonatal infection or sepsis, intravenous therapy needed hypoglycaemia, wet lung syndrome, meconium aspiration syndrome, pneumothorax and/or pneumomediastinum, periventricular leucomalacia, convulsions and other neurological abnormalities necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH) or asphyxia. Adverse neonatal outcome will be defined as a 5-minute Apgar score below 7, an umbilical artery pH below 7.05 or admission to the neonatal intensive care.

Power/data analysis: We plan to have 700 inclusions.

Time schedule: Anticipated study end Summer 2013

Publications Langenveld J, Jansen S, van der Post JA, Wolf H, Mol BW, Ganzevoort W. Recurrence risk of a delivery before 34 weeks of pregnancy due to a severe hypertensive disorder: a systematic review. *Am J of Perinat.* 2010 Aug; 27 (7): 565-71.

Langenveld J, Buttlinger A, van der Post JA, Wolf H, Mol BW, Ganzevoort W. Recurrence risk and prediction of a delivery under 34 weeks after a history of a severe hypertensive disorder. *BJOG* 2011 Feb 4.

Presentations September 2008 16th World Congress ISSHP, Washington. Langenveld et al. Outcome of subsequent pregnancy of women with severe hypertensive disorders before 34 weeks of gestation in the first (index) pregnancy. Oral presentation

Oktober 2010 17th World Congress ISSHP, Melbourne. Langenveld et al. Neonatal outcome of pregnancies complicated by hypertensive disorders between 34 and 37 weeks of gestation. Young investigator travel award. Oral presentation

HTA Long term outcome

ZonMw 80-82310-98-08208

HTA Long-term economic and health-related consequences of short term outcomes in evaluation of perinatal interventions

Arts-onderzoeker: Drs. M. Teune AMC

Projectleiding: Dr. B.C. Opmeer AMC

Evaluation of perinatal interventions requires assessment of both maternal as well as neonatal outcomes. Since serious neurological sequelae from perinatal complications become manifest only after several years, appropriate assessment of neonatal outcome requires follow-up of the child of at least 2 years and preferably even longer. However, such follow-up is expensive, and falls outside the funding for the limited period of time of most research programs.

As a consequence, in many prospective studies in perinatal medicine neither long-term health nor economic consequences can be addressed, or they are described qualitatively rather than integrated quantitatively in the economic analyses. Instead, intermediary and/or short term outcomes are reported, for which long term clinical and economic implications are only implicitly known.

Examples of such pertinent intermediary outcomes are unintended multiple pregnancy, preterm delivery, and caesarean section. Short term perinatal outcomes associated with these intermediary outcomes are for example respiratory distress syndrome, neonatal sepsis or maternal blood loss and puerperal infections.

Long term consequences of a short term perinatal outcome may be different in case of a multiple pregnancy, a preterm delivery or a preterm multiple birth. Multivariable prediction models can be used to estimate long term consequences of a short term outcomes in combination with history and intermediary outcomes. Such estimates (including model uncertainties) could subsequently be integrated in future evaluations of perinatal interventions, thereby increasing both efficiency as well as validity.

This study aims to develop long term prediction models for the following short term perinatal outcomes: respiratory distress syndrome, bronchopulmonary disease, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, sepsis, asphyxia, severe umbilical cord acidemia, uneventful birth and caesarean section.

These models will be developed using data from a cohort study of preterm and/or SGA children born in 1983, for which follow-up assessments were done at ages 2, 5, 9, 10, 14 and 19. Internal validation will be performed to correct for bias due to overfit. Other datasets containing relevant outcome assessments at the medium term will be used to externally validate these models.

Publications: Teune MJ, van Wassenaer AG, Mol BW, Opmeer BC. Long-term health-related and economic consequences of short-term outcomes in evaluation of perinatal interventions. *BMC Pregnancy Childbirth*. 2010 Aug 10;10:42.

HTA Value of information

ZonMw 80-82325-98-8011

HTA Long-term economic and health-related consequences of short term outcomes in evaluation of perinatal interventions

Arts-onderzoeker: Drs. J.Y. Vis AMC

Projectleiding: Dr. B.C. Opmeer AMC

The aim of diagnostic and screening tests in health care is to reduce diagnostic uncertainty for both health care providers and patients. The contribution of testing is predominantly evaluated in terms of their ability to support treatment decisions in order to improve health outcomes (diagnostic value). This approach implies a bias against testing, as value is only attached to its ability to support subsequent treatment decisions and associated ultimate health consequences. In daily clinical practice, however, testing is also beneficial as tests inform patients and clinicians, regardless of eventual treatment decisions.

At present, the available evidence concerning this value of information in diagnostic test evaluation is very limited. The question is whether tests should be valued on their diagnostic value alone or that patients and/or doctors put additional value to the information concerning the test results (knowing for the sake of knowing).

This HTA methodology project aims to assess whether and to what extent patients and doctors attach additional value to the information resulting from diagnostic tests (value of information), aside from their diagnostic value and how this can be incorporated in subsequent health policy decisions or clinical practice guidelines.

The strategy encompasses three parts:

1. development of an instrument to measure the value of information of diagnostic tests, based on a brief review of the literature followed by interviews with patients and professionals to identify which factors they consider and trade-off in the evaluation of diagnostic tests. Based on these results, an instrument will be developed in which these factors are incorporated.

2. the instrument will be evaluated empirically for psychometric properties, followed by a clinical interpretation of the results.

3. Finally, we will identify an effective and feasible approach to incorporate this additional outcome in future diagnostic test evaluations.

If participants are found to attach value of information to test results, in addition to the diagnostic value, our study demonstrates the relevance of this aspect in diagnostic test evaluation. In addition, the instrument developed in our study would also enable future diagnostic studies to assess the value of information in a more standardized way. Finally, experts advice will be summarized on how this value of information aspect could be incorporated in clinical or health policy decisions.

Presentations: Additional effects of the cervical length measurement in women with preterm contractions: a systematic review. Vis JY, Kuin RA, Grobman WA, Mol BW, Bossuyt PM, Opmeer BC. Arch Gynecol Obstet. 2011 Apr 12. [Epub ahead of print]

INeS



Promovendus Drs. A. Bensdorp
Project leaders Dr. F. van der Veen, dr. M. van Wely
ZonMw: 120620027
Nederlands Trial Register: NTR939

Prevention of multiple pregnancies in couples with unexplained or mild male subfertility

A randomized trial to evaluate whether MNC-IVF or IVF-eSET reduces multiple pregnancies as compared to IUI-COH in couples with unexplained subfertility or mild male subfertility and poor fertility prospects.

Background Currently couples with unexplained or mild male subfertility and a poor prognosis are treated with intra uterine insemination (IUI) and controlled ovarian hyperstimulation (COH). After 6 cycles of unsuccessful IUI-COH, these couples are subsequently treated with in vitro fertilisation (IVF) and double embryo transfer (DET). With this treatment 10-20% of the achieved pregnancies is multiple pregnancy. These are high risk pregnancies with regard to the obstetrics and the neonatal outcomes. Premature birth, growth retardation and pre eclampsia are the most frequent complications. These result higher medical costs. It is unclear whether alternative treatments such as modified natural cycle MNC-IVF, or IVF with elective single embryo transfer (eSET) for this population selection result in comparable pregnancy rates, and simultaneously reduce the number of multiple pregnancies. Generally, patients consider IVF as a more intense treatment than IUI.

Objective Our main objective is to prevent multiple pregnancies and the concomitant neonatal mortality and morbidity while retaining acceptable delivery rates in couples with unexplained subfertility or mild subfertility with poor fertility. Furthermore, we intend to evaluate the preference of couples for the treatments and assess how couples value a twin as outcome, compared to a singleton pregnancy or no pregnancy. Also the costs of the treatment, follow up, delivery and maternal and perinatal hospital care until six weeks after delivery are evaluated.

Study Design The study design is a multi centred randomized clinical trial

Population Couples with unexplained infertility or mild male infertility with poor fertility prospects. Female age must be between 18 and 38 years.

Intervention

- Intra uterine insemination (IUI) with stimulation
- In Vitro Fertilisation with transfer of one embryo (IVF-eSET)
- In Vitro Fertilisation with a modified natural cycle (IVF-MNC)

Randomisation (lottery) will determine whether a couple will start with either 6 stimulated IUI cycles or 3 IVF e SET cycles or 6 IVF MNC cycles.

Outcomes Primary outcome measurements in all groups is life birth of a child. Secondary outcomes are multiple pregnancies, clinical pregnancies, pregnancy complications such as pre-eclampsia, and a cost analysis and patient satisfaction.

Time schedule Start in 2009, anticipated study end mid 2013

Publications: Bensdorp AJ, Slappendel E, Koks C, Oosterhuis J, Hoek A, Hompes P, Broekmans F, Verhoeve H, de Bruin JP, van Weert JM, Traas M, Maas J, Beckers N, Repping S, Mol BW, van der Veen F, Van Wely M The INeS study: prevention of multiple pregnancies: a randomized controlled trial comparing IUI COH versus IVF e SET versus MNC IVF in couples with unexplained or mild male subfertility. BMC Womens Health. 2009 Dec 18;9:35



Project leaders Drs. H. Torrance, Prof. dr. F.J.M. Broekmans

ZonMw: 171102019

Nederlands Trial Register: NTR2745

Significance of routine Hysteroscopy prior to a first IVF Treatment cycle / the inSIGHT trial

Objective

The aim of the study is to assess whether diagnosing and treating unsuspected intrauterine abnormalities by additional diagnostic tests (saline infusion sonography (SIS) and/or routine office hysteroscopy) prior to a first IVF/ICSI treatment cycle improves IVF outcome and with that the cost-effectiveness of the fertility treatment.

Study design

Patients scheduled for a first IVF/ICSI treatment will undergo randomization for routine fertility work-up or routine work-up plus diagnostic tests to evaluate the uterine cavity (hysteroscopy alone or hysteroscopy in combination with SIS). On-the-spot-treatment of detected intrauterine abnormalities will be carried out during the hysteroscopy. In both study arms, IVF/ICSI treatment will be initiated. Also, the patients' tolerance and preferences will be investigated. Finally, a cost-analysis based on the study results will be performed.

Study population

In total 738 patients indicated for a first IVF/ICSI treatment cycle at one of the participating hospitals will be included in this study.

Outcome measures

Main study outcome:

Cumulative ongoing pregnancy rate resulting in live birth achieved within 18 months of IVF/ICSI treatment after randomization (obtained in treatment cycles with fresh embryos as well as in subsequent cryo/thaw cycles).

Secondary study outcomes:

- Cumulative implantation rate and miscarriage rate achieved within 18 months of IVF/ICSI treatment after randomisation (obtained in treatment cycles with fresh embryos as well as in subsequent cryo/thaw cycles)
- Cumulative miscarriage rate within 18 months of IVF/ICSI treatment after randomization (obtained in treatment cycles with fresh embryos as well as in subsequent cryo/thaw cycles)
- Cost calculations of SIS, hysteroscopy procedures and the IVF treatment
- Patient tolerance of a SIS and diagnostic/therapeutic hysteroscopy procedure

Power/data analysis

In cases that are treated for the predefined abnormality, the increase in ongoing pregnancy after the subsequent cycle of IVF/ICSI is found to be 9-32% in patients with recurrent IVF failure). In a group of patients indicated for a first IVF/ICSI treatment cycle, the difference in cumulative live birth rate after 18 months of IVF/ICSI treatment is estimated to be 10% between the patients with and without hysteroscopy (40 versus 30%). The number of patients needed to have 80% power (with alpha = 0.05) to detect such a difference is 350 per study arm. In order to allow for a dropout rate of 5%, a total of 738 patients (700/0.95) will be required. From previous literature, we consider the prevalence of unsuspected intrauterine abnormalities to be 12% and the sensitivity of SIS compared to hysteroscopy to be 95%. To achieve a 95% confidence interval (CI) of 10% (85-100%) we would need to perform SIS and hysteroscopy in 160 patients. This means a total of 320 patients need to be randomized for SIS + hysteroscopy or routine work-up.

IVM study

Project leader Dr. J. de Bruijn
Promovendus Drs. S. Braam
ZonMw: 171101010
Nederlands Trial Register: NTR2375

In vitro maturatie

Background

Current ART requires COH to increase the number of oocytes. COH can lead to OHSS. In IVM immature oocytes are harvested from the ovaries without COH and matured in vitro in approximately 30 hours. These in vitro matured oocytes can be fertilised by IVF or ICSI. The first IVM-pregnancy was reported in 1991. It is estimated that since then over 1100 IVM children have been born worldwide.

In recent years the IVM technique has become increasingly effective. In observational studies the delivery rate of an IVM cycle was 10-15%. Due to the absence of COH IVM has a potential benefit for patients with an increased risk of developing OHSS, such as PCOS-patients. These potential benefits extend to patient friendliness and reduced costs.

Objectives Primary objective: To evaluate the cumulative live birth rate for two treatment strategies: 2 IVM/ICSI cycles versus 1 COH/IVF or COH/ICSI cycle. Secondary Objectives: To evaluate the health and development of IVM/ICSI children versus COH/IVF/ICSI children in 5 years' follow up program. To evaluate the number and nature of adverse events during or following the two treatment strategies. To evaluate the direct and indirect costs of the two treatment strategies. To evaluate patients' quality of life during and after the two treatment strategies.

Study design Multicentre randomised clinical trial in 400 couples. The trial will be preceded by a pilot study of 50 non-randomised IVM cycles for implementation of the technique.

Study population PCOS patients indicated for IVF or IVF and ICSI patients who experienced an (imminent) OHSS in an earlier COH cycle.
Age between 18 and 38 years.

Intervention 2 IVM/ICSI cycles or 1 COH/IVF or COH/ICSI cycle.

Outcome measures

Cumulative live birth rate after IVM/ICSI or COH/IVF/ICSI strategy.



Promovendus Drs. M.J. Rutten
Project leader Dr. M.R. Buist, gynaecologist-
oncologist AMC Amsterdam
ZonMw: 80-82310-97-11056
Nederlands Trial Register: NTR2644

Laparoscopy to predict the result of primary cytoreductive surgery in advanced ovarian cancer patients

Objective

To investigate whether laparoscopy is cost-effective in predicting which patients will benefit from primary surgery and which patients should be treated with neoadjuvant chemotherapy and interval surgery instead.

Study design

A multicenter prospective randomized trial

Study population

Women between 18-80 years suspected of having advanced stage ovarian carcinoma (FIGO >IIB), who are eligible for primary debulking surgery after conventional staging and have given written informed consent

Intervention

We will randomly assign patients after conventional staging to either primary surgery, without laparoscopy, or to additional laparoscopy to guide the decision between primary surgery followed by chemotherapy and neoadjuvant chemotherapy plus interval surgery

Outcome measures

Primary outcome will be futile laparotomy, defined as suboptimal primary cytoreductive surgery, when the diameter of the largest residual tumor metastasis at the end of surgery is more than 1 cm.

Secondary outcomes will be no residual tumor, less than 1 cm residual tumor after cytoreductive surgery, progression free survival, overall survival, morbidity, quality of life, days in hospital and costs.

Power/data analysis

The present rate of optimally operated patients in the Netherlands is only 37-59%. Therefore, the rate of suboptimal primary debulking after conventional staging in the Netherlands is estimated to be at most 40%, after laparoscopy this should be less than 20%. With a two-sided significance level of 0.05, and a power of 80%, 90 patients per arm have to be included. Considering 10% loss, we plan to enroll 200 patients.

Economic evaluation

The key question in the economic evaluation is to assess whether the laparoscopy can reduce the number of futile primary surgeries, and associated costs to an extent that at least offsets the costs of this laparoscopy in all eligible patients. A strategy that reduces the number of unnecessary laparotomies is considered preferable, even if this does not improve survival, also if the costs generated by both strategies are comparable. The economic evaluation will be performed from a societal perspective including direct and indirect medical costs. We hypothesize that additional costs of laparoscopies are greatly offset by the reduced number of futile laparotomies.

Time schedule

First year: start of study in all participating centers. First 30 months: inclusion of patients, data collection and entry. Last 6 months: analysis of data, preparation of manuscripts

Lifestyle



Promovendus Drs. M. Mutsaerts
Project leaders Dr. A. Hoek, dr.ir. W. Bemelmans
ZonMw: 50-50110-96-518
Nederlands Trial Register: NTR1530

Costs and effects of a structured lifestyle program in overweight and obese subfertile couples to prevent unnecessary treatment and improve reproductive outcome.

Rationale Subfertility affects approximately one in ten couples planning conception. Among subfertile women, about 30% are overweight or even obese. Epidemiological data suggest that the reduction of overweight will increase the chances of conception, decrease pregnancy complications and improve perinatal outcome. In small intervention studies beneficial reproductive effects of improvement of lifestyle leading to a reduction in body weight have been demonstrated. The British Fertility Society advises that fertility treatment be withheld if the body mass index (BMI) is over 35.

In the Netherlands, there is at present no agreed standard of care for subfertile women with overweight or obesity. Some centres simply withhold treatment of couples in whom the woman is overweight or obese, but most fertility centres treat overweight or obese women irrespective of their BMI. In a few centres, support is offered to women to help them lose weight.

Objective We compare the costs and effects of a six months structured lifestyle program, aimed at weight loss, to "usual care". The intervention aims to prevent unnecessary fertility treatment, complications associated with fertility treatment and obesity related pregnancy complications, thus improving pregnancy chances and perinatal outcome.

Study design Multicenter randomised clinical trial.

Study population Subfertile women (age 18-38) with a BMI between 29 and 40.

Intervention The intervention consists of a structured lifestyle program of six months, which aims at realistic weight loss of at least 5% to 10%. Following six months of lifestyle intervention patients will start fertility treatment as indicated in the "usual care" group. In the "usual care" arm fertility treatment will be started if this is justified by the individual prognosis (guideline NVOG)

Main study parameter Primary endpoint is the birth of a healthy singleton after vaginal delivery of at least 37 weeks gestation.

Study duration Preparation of the study, including the training of the nurses, will take three months. Inclusion of the couples will take 24 months and the lifestyle intervention will take six months. Follow up is continued for 24 months after randomisation. Database cleaning and analysis of the study will take 6 months. Duration of the study: 57 months

Start in 2009, anticipated study end mid 2013

Publications Mutsaerts MA, Groen H, Bogt Ter NC, Bolster JH, Land J, Bemelmans W, Kuchenbecker WK, Hompes PG, Macklon NS, Stolk RP, van der Veen F, Maas J, Klijn NF, Kaaijk EM, Oosterhuis GJ, Bouckaert PX, Schierbeek JM, van Kasteren YM, Nap AW, Broekmans FJ, Brinkhuis EA, Koks CA, Burggraaff JM, Blankhart AS, Perquin DA, Gerards MH, Mulder RJ, Gondrie ET, Mol BW, Hoek A. The LIFESTYLE study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. A randomised controlled trial. *BMC Womens Health*. 2010 Jun 25;10(1):22

METEX



Promovendus Drs. N. van Mello

Project leaders Dr. P. Hajenius, dr. B.W. Mol

ZonMw Clinical fellow grant 40-00703-97-05-154

Nederlands Trial Register: NTR611

Methotrexate versus Expectant management in women with ectopic pregnancy

Background

The incidence of ectopic pregnancy (EP) is approximately 1-2 % of all pregnancies. An early diagnosis is possible by transvaginal sonography (TVS) in combination with serum hCG measurements. In the medical treatment of EP, systemic methotrexate is the drug of choice. In several randomised controlled trials systemic methotrexate has been shown to be an effective treatment in selected patients with EP. Expectant management has been practiced, based on the acknowledgement that many early EPs ultimately result in tubal abortion or reabsorption. Ten percent of women presenting with suspected EP have low and plateauing serum hCG concentrations. These women are often treated with systemic methotrexate. However, there is no evidence on the effects of treatment in this particular subgroup of women

Objective To study whether in women with EP with low but plateauing serum hCG concentrations treatment with systemic methotrexate in a single dose intramuscular regimen is superior over expectant management in terms of treatment success, future pregnancy, health related quality of life and costs.

Study-design Multicenter randomised controlled trial in 13 participating centers in The Netherlands.

Population All hemodynamically stable patients ≥ 18 years with either on TVS a visible EP and a plateauing serum hCG concentration $< 1,500$ IU/L or with a pregnancy of unknown location (PUL) and a plateauing serum hCG concentration $< 2,000$ IU/L (persisting PUL) will be eligible for the trial. Patients with a viable EP, signs of tubal rupture or active intra abdominal bleeding, or a contra-indication for methotrexate will not be included. Randomisation will be carried out by an internet based randomisation.

Intervention and follow up Systemic methotrexate in a single dose intramuscular regimen (1 mg/kg body weight) will be compared with expectant management in an outpatient clinical setting. Serum hCG levels will be monitored weekly. In case of inadequately declining serum hCG concentrations and/or clinical symptoms treatment (methotrexate or surgery) will be installed. Quality of Life will be assessed before, during and after treatment by questionnaires. Future fertility will be assessed by questionnaires after 6, 12, 18 and 24 months.

Outcome measures and analysis The primary outcome measure is an uneventful decline of serum hCG to an undetectable level. Secondary outcomes are number of (re)interventions (additional methotrexate and/or surgery), treatment complications, health related quality of life, future fertility, and financial costs. The analysis will be performed according to the *intention to treat* principle. Moreover, patients' preferences will be assessed.

Time path Start in April 2007, anticipated study end ultimo 2011

Publications: The METEX study: methotrexate versus expectant management in women with ectopic pregnancy: a randomised controlled trial. van Mello NM, Mol F, Adriaanse AH, Boss EA, Dijkman AB, Doornbos JP, Emanuel MH, Friederich J, Leeuw-Harmsen L, Lips JP, van Santbrink EJ, Verhoeve HR, Visser H, Ankum WM, Veen F, Mol BW, Hajenius PJ. BMC Womens Health. 2008 Jun 19;8:10.

M-OVIN'



Promovendus Drs. M.J. Nahuis

Project leaders Dr. J. Oosterhuis, dr. P. Hompes, dr. B.W. Mol

Nederlands Trial Register: NTR1449

Treatment alternatives for subfertile women with class II anovulation not conceiving after six ovulatory cycles with clomiphene citrate: A randomized controlled trial.

Background

Ovulation induction with Clomiphene citrate (CC) is the first line of treatment in women with WHO class II anovulation. Whereas almost 80% of these patients ovulate after CC, only 40 to 50% conceive. When unsuccessful in conception, treatment can be proceeded with gonadotropins. CC treatment is associated with a 8% risk of multiple gestation, whereas treatment with gonadotropins is associated with a risk of 30-40 %. At present, it is unclear for how many cycles ovulation induction with CC should be repeated, and when to switch to ovulation induction with gonadotropins and/or add of intra-uterine insemination.

Objective

The purpose of this study is to assess the effectiveness of extended treatment with CC compared to treatment with gonadotropins and/or the use of intra-uterine insemination (IUI), in patients who had six ovulatory cycles after CC, but did not conceive.

Study design

Randomized controlled trial.

Setting

20 fertility centers in The Netherlands.

Study population

Subfertile women with WHO class II anovulation who are ovulatory on CC, but have not conceived in 6 ovulatory cycles.

Intervention

Patients will be randomly allocated to four treatment arms: extended CC treatment for 6 months, ovulation induction with gonadotropins for 6 months, extended CC treatment with IUI for 6 months and ovulation induction with gonadotropins with IUI for 6 months

Main outcome measures

Pregnancy leading to live birth.

Power calculation

The analysis will be by intention to treat. Two comparisons will be made, one in which CC is compared to gonadotropins and one in which the addition of IUI is compared to ovulation induction only. Assuming an increase from 20%, 200 patients are needed to be included, i.e. 100 per arm (alpha .05, beta .80).

Time schedule

Start in December 2008, anticipated study end mid 2012

OPTIMIST



Project leaders Prof.dr. F.J.M. Broekmans, Dr. H. Torrance
ZonMw 171102020
Nederlands Trial Register: NTR2657

Optimisation of cost effectiveness through individualised FSH Stimulation dosages for IVF treatment

Objective

The present study will assess the cost-effectiveness of routine use of ovarian reserve tests (ORTs) and subsequent use of individualised FSH dosages in predicted poor and hyper responders as compared to a policy without ORT using standard dosages of FSH.

Study design

The study will be designed as a large nationwide multicenter cohort study, with two RCTs embedded in this cohort. The cohort will consist of 1,500 women screened for ovarian capacity by an antral follicle count (AFC) prior to starting IVF treatment.

Study population

Patients will be recruited from the list of IVF/ICSI indicated couples in 15 hospitals with a special interest in infertility care.

Intervention

Patients with predicted poor response (AFC below 10) will be randomly allocated to a treatment strategy based on an increased FSH dose versus standard FSH dose. All study and control participants will undergo a maximum of three cycles during a treatment period of maximally 18 months.

Patients with predicted hyper response (AFC more than 15) will be randomly allocated to a treatment strategy based on decreased FSH dose versus standard FSH dose.

Outcome measures

Main study outcomes:

Ongoing pregnancy resulting in live birth within 18 months after randomisation. These pregnancies can be obtained in treatment cycles with fresh embryos, as well as in subsequent cryo/thaw cycles after completion of any fresh stimulation cycle. Spontaneous pregnancies between treatment cycles will also be taken into account.

Costs of treatment: direct medical costs, direct non-medical costs and indirect costs

Secondary study outcomes:

Number of oocytes

Poor response

Hyper response

OHSS grade 2 and 3

Cycle cancellation for hyper and poor response, multiple pregnancy, total IU of FSH applied per stimulation cycle

Power/data analysis

We need to include a cohort of 1,500 women for ovarian reserve screening using the AFC, in order to achieve the numbers of cases needed for the two trials. This will then allow a sample size of just over 300 women for the poor response trial (RCT1).

For RCT2 an increase in pregnancy rate from 35% to 42% over three cycles can be expected. With 300 participants the power to detect this difference is 24%.

POMPOEN

Promovendus Drs. M.C. Breijer, AMC Amsterdam
Projectleider: Prof.dr. B.W. Mol
Nederlands Trial Register NTR2130

Effectiveness of saline-infused sonography and hysteroscopy in the work-up for postmenopausal bleeding.

Rationale

Postmenopausal bleeding occurs in approximately 15,000 women per year, and may signal serious underlying medical problems. The Dutch guideline on the work-up for postmenopausal bleeding emphasises diagnosing malignant pathology of the endometrium. Transvaginal sonography is used to measure endometrial thickness, if the endometrial thickness measures more than 4 mm, endometrium aspiration (using a Pipelle) is advocated to rule out or diagnose endometrial carcinoma. When malignancy has been ruled out, it is uncertain whether the work-up should be continued with SIS and/or hysteroscopy (and subsequent polypectomy when an abnormality is detected), if at all. The present proposal will study the effects of these strategies. The proposal will consider medical effectiveness.

Objective

SIS and hysteroscopy in the work-up for postmenopausal bleeding will be studied. Medical effectiveness in terms of treatment of the postmenopausal bleeding will be evaluated. To assess which women need saline-infused sonography and/or hysteroscopy, if at all, we will answer the following questions:

What are the effects of the following strategies:

1. no further testing after carcinoma has been ruled out
2. SIS for all patients, and hysteroscopy after abnormal SIS
3. immediate hysteroscopy for all patients
4. targeted selection of patients at increased risk for polyps.

Study design

Multicenter randomized trial.

Study population

Patients with postmenopausal bleeding and an endometrial thickness of more than 4 mm, in whom through endometrial biopsy malignancy could be ruled out.

Intervention

Patients will be randomised for a subsequent diagnostic work-up with SIS and hysteroscopy or no further diagnostic work-up. In case the patient is allocated to no diagnostic work-up, she will be sent home without further diagnostic tests. She will be instructed to contact the gynaecologists in case of recurrence of vaginal bleeding.

Outcome measures

Primary outcome: Recurrence of postmenopausal bleeding.

Power/data analysis

We expect the probability of recurrence of menstrual bleeding without SIS/hysteroscopy to be 40%. A strategy with SIS/hysteroscopy is thought to reduce this percentage to 20% to make such a strategy cost-effective. We anticipate a drop-out rate of the study of 20%. When we use a two-sides test, we need 200 patients randomised to two groups of 100 patients to show such a difference (alpha error .05, beta error .20)

PreCare



Promovendi:

Sander van Kuijk, Maastricht UMC

Denise Delahaye, Maastricht UMC

Projectleider: Dr. L. Smits, Maastricht UMC

Clinical trials register NVT **ZonMW** 17088.2303

Cost-effectiveness of recurrence-risk guided care of pregnant women with preeclampsia or HELLP in the previous pregnancy

Objective

Objective of the PreCare study is to assess the cost-effectiveness of recurrence-risk guided care versus care as usual in pregnant women who suffered from preeclampsia or HELLP in their first pregnancy.

Study design

The PreCare study is a partly retrospective and partly prospective multicenter cohort study. For the economic evaluation, a modeling approach will be used.

Study population

The study population consists of pregnant women with preeclampsia/HELLP in their previous pregnancy, to be recruited from five academic and six peripheral hospitals. We aim to include approximately 250 patients in the prospective arm of the study (recurrence-risk guided follow-up arm). These patients will be compared with an equal number of comparable patients from the recent past (care-as-usual arm).

Inclusion criteria

1. Presentation before 17 weeks' gestation;
2. Preeclampsia or HELLP diagnosed in the previous pregnancy;
3. Measurements between 3-9 months postpartum, of at least HOMA-IR, MAP and HDL;
4. Informed consent.

Intervention

The intervention in the PreCare study is the referral to either High Care (HC) or Medium Care (MC), depending on predicted risks of developing severe preeclampsia/HELLP or delivery of an infant with extremely low birth weight. HC comprises 17 visits to the outpatient clinic, ultrasonographic fetal biometry during each visit, additional diagnostics in weeks 12, 16 and 20, and the possibility of a 1-week in-hospital diagnostic stage. MC consists of 11 visits accompanied by fetal biometry, and no additional diagnostics.

Outcome measures

Primary outcome measure is the occurrence of either severe preeclampsia or HELLP (requiring delivery before 34 weeks) or delivery of an infant with extremely low birth weight (<1250 g) among women in the MC group. Secondary outcome measures are timing and occurrence of preeclampsia, eclampsia or HELLP, IUGR, caesarian section, admission to NICU, pregnancy duration, maternal/ infant mortality, societal costs, QoL, anxiety, depression, posttraumatic stress, satisfaction with treatment and non-compliance.

Economic evaluation Costs and effects of recurrence-risk guided care and care-as-usual will be compared by means of a decision model. Two incremental cost-effectiveness ratios will be calculated: 1) cost per Quality Adjusted Life Year (mother is the unit of analysis) and 2) cost per live born child (child is the unit of analysis).

Publications Cost-effectiveness of recurrence risk guided care versus care as usual in women who suffered from early-onset preeclampsia including HELLP syndrome in their previous pregnancy (the PreCare study). Delahaije DH, van Kuijk SM, Dirksen CD, Sep SJ, Peeters LL, Spaanderman ME, Bruinse HW, de Wit-Zuurendonk LD, van der Post JA, Duvekot JJ, van Eyck J, van Pampus MG, van der Hoeven MA, Smits LJ. BMC Pregnancy Childbirth. 2010 Oct 11;10:60.

PROBAAT II



Promovendus Drs. M. ten Eikelder

Projectleiders: Dr. K.W.M. Bloemenkamp LUMC, dr. B.W. Mol
AMC

Clinical trials register NNB

Funding: Nuts-Ohra

Objective

To assess in term pregnant women with an unfavourable cervix (Bishop score < 6) the effectiveness, cost efficient and most patient friendly way of induction of labour with a transcervical Foley catheter as compared to induction with misoprostol.

Study design

Multicentre prospective randomised controlled trial. The study will be performed within a consortium of perinatal centres, that are collaborating in several proposed studies.

Study population

Term pregnant women with an indication for induction of labour

Intervention [or: Methods]

Induction of labour with a transcervical Foley catheter compared to intravaginal misoprostol.

Inclusion Criteria:

- Term pregnancy (>37 weeks of pregnancy)
- Scheduled for induction of labour
- Vital singleton pregnancy
- Intact membranes
- Unfavourable cervix (Bishop score < 6)
- Cephalic presentation

Exclusion criteria:

- Previous caesarean section
- Placenta praevia
- Hypersensitivity for one of the products used for induction

Outcome measures

The primary outcome will be a composite of complications of uterine hyperstimulation, i.e. asphyxia and fluxus post partum. Secondary outcomes will include mode of delivery, costs and patient satisfaction.

Power/data analysis

Analysis will be by intention to treat. We need two groups of 721 women (1442 women) to demonstrate a reduction in fluxus and neonatal admission from 10% to 6%.

Economic evaluation

For each of the two strategies, we will calculate costs of perinatal care. In case of equal neonatal and maternal outcome the analysis will be a cost-minimisation analysis.

Time schedule

30 months. Three months preparation. Twenty-four months inclusion. Three months analysis and report.

PROBAAT-S



Promovendus Drs. C.M.A. Huisman
Projectleider: Dr. K.W.M. Bloemenkamp LUMC
Clinical trials register n.v.t.
Funding: not funded

Objective

To study the methods of induction of labour in women with a previous caesarean section and their respective effectiveness and safety, i.e. neonatal and maternal morbidity in the Netherlands.

Study design

A national prospective observational cohort study.

Study population

Term pregnant women with a history of one previous caesarean section and an indication for induction of labour in the current pregnancy.

Methods

All women with one previous caesarean section and an indication for induction of labour will be treated according to their local hospital protocol who may induce by prostaglandins, Foley catheter or amniotomy. Hospitals that do not induce labour in this group of women perform a repeat caesarean section. All women will be registered and information concerning their (obstetrical) history, pregnancy, mode of delivery and puerperium will be collected as well as neonatal data. All data will be collected in a web-based file.

Outcome measures

Primary outcome will be neonatal and maternal morbidity. Secondary outcome measures will be mode of delivery, including subanalysis of Foley catheter versus prostaglandins, induction-to-delivery interval and costs.

Inclusions

We aim to include 1500 women in a two-year period starting on August 1st 2011.

Time schedule

36 months. 6 months preparation, 24 months inclusions, 6 months data analysis.

PROMISE



Promovendus Drs. Y.E.M. Koot
Projectleider: Dr. M. Goddijn, AMC
Clinical trials register ISRCTN:92644181
Funding: NIHR HTA 08/38/01

PROgesterone in recurrent MIScarriagE

Objective

To assess improvement in live birth rate after progesterone supplementation. In the absence of properly randomized controlled trials that assessed the efficacy of progesterone in women with RM, a clinical trial with adequate randomization is necessary. In clinical practice, women with RM are frequently seeking advice about the indication for progesterone treatment. Therefore, we have designed a randomized clinical trial to assess the efficacy of progesterone, as compared with placebo, on the live birth rate in women with at least 3 preceding miscarriages.

Study design

Randomized, double-blind, placebo controlled multicentre study

Study population

Women with recurrent miscarriage, i.e. at least 3 miscarriages, aged 18-39 years, conceiving spontaneously

Intervention

One group receives vaginal progesterone pessaries 2x 200 mg twice daily (Utrogestan®) and the other group receives placebo pessaries of identical appearance twice daily.

Outcome measures

Primary: Live birth rate.

Secondary: Miscarriage rate, gestational age at delivery, adverse events, serum progesterone luteal phase.

PROMISES

Promovendi Drs. C. Beijers, drs. J.L. Meijer, T. Verbeek

Project leader Dr. H. Burger, UMC Groningen

ZonMw: 120520013

Nederlands Trial Register: NTR2242

Pregnancy Outcomes after Maternity Intervention for Stressful Emotions

Introduction

How is the development of the children of women who have suffered from symptoms of depression and/or anxiety during pregnancy? And what will happen regarding the psychosocial development of child and mother therapy is offered to these women during pregnancy?

Rationale:

Maternal depression or anxiety during pregnancy is a risk factor for adverse psychosocial outcomes in the offspring. To date, however, no previous study has demonstrated that treatment of depressive or anxious symptoms in pregnancy actually could prevent psychosocial problems in children. Preventing psychosocial problems in children will eventually bring down the huge public health burden of mental disease.

Objective:

To assess the effects of Cognitive Behavioral Therapy (CBT) in pregnant women with symptoms of anxiety or depression on the child's behavioral/emotional problems. In addition, we aim to study its effects on the child's development, maternal mental health, and neonatal outcomes, as well as the cost-effectiveness of CBT relative to usual care.

Study design:

Single blind randomized controlled trial.

Study population:

300 women with at least moderate levels of anxiety or depression at the end of the first trimester of pregnancy. By including 300 women we will be able to demonstrate effect sizes of 0.35 or over on the total problems scale of the CBCL 1.5-5 with alpha 5% and power (1-beta) 80%.

Intervention:

10-14 individual CBT sessions, 6-10 sessions during pregnancy and 4-8 sessions after delivery (once a week), or care as usual.

Main study parameters/endpoints:

Primary:

Behavioral/emotional problems at age 1.5 as assessed by the total problems scale of the Child Behavior Check List 1.5 "C 5 years.

Secondary:

Mental, psychomotor and behavioral development of the child at age 18 months according to the Bayley scales; Maternal anxiety and depression during pregnancy and 6 weeks postnatal; Maternal attachment style; Neonatal outcomes: birth weight, gestational age and Apgar score; Health care consumption and general health status (economic evaluation).

Time schedule:

After inclusion, follow-up takes 6 months during pregnancy and 18 months following delivery, 24 months in total.

Pessaries in multiple pregnancy as a prevention of preterm birth

Objective To investigate the hypothesis that prophylactic use of a cervical pessary will be effective in the prevention of preterm delivery and the neonatal mortality and morbidity resulting from preterm delivery in multiple pregnancy. We will evaluate the costs and effects of this intervention.

Study design Multicenter randomised study.

Study population

All women presenting with a multiple pregnancy (monochorionic and bichorionic) between 12 and 20 weeks of gestation are eligible for the study.

Intervention Eligible women will be randomly allocated to receive either a pessary or no treatment. *Treatment group:* The cervical pessary will be inserted any time between 12 and 20 weeks and continued till delivery or 36 weeks gestation, whichever comes first.

Control group: No treatment for cervical incompetence will be given.

Outcome measures

Primary outcomes

The main outcome parameter is the composite morbidity rate of children in the two groups. This composite morbidity rate contains the following variables: severe Respiratory Distress Syndrome (RDS), Broncho Pulmonal Dysplasia (BPD), Intraventricular Haemorrhage II B or worse, Necrotizing Enterocolitis (NEC), proven sepsis and death before discharge from the nursery. They will be measured until 10 weeks after the expected term date.

Secondary outcomes

Secondary outcome measures are time to delivery, preterm birth rate before 32 and 37 weeks, days of admission in neonatal intensive care unit, maternal morbidity, maternal admission days for preterm labour and costs.

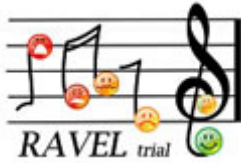
Power/data analysis The effectiveness of a cervical pessary versus no treatment will be assessed by calculating relative risks and 95% confidence intervals. Assuming a decrease of the incidence of bad neonatal outcome from 7.2 % without to 3.9% with a cervical pessary, using a two-sided test with an alpha of 0.05 and a power of 0.80 we need 330 women in the control group and 330 in the intervention group (660 women in total).

Time schedule Duration of the study will be 48 months. We will need a run-in period of three months for the study set up. Thirty-eight months for inclusion of the required number of cases. Seven months for follow-up data collection and report of results.

Publications

Hegeman MA, Bekedam DJ, Bloemenkamp KWM, Kwee A, Papatsonis DNM, van der Post JAM, Lim AC, Scheepers HCJ, Willekes C, Duvekot JJ, Spaanderman M, Porath M, van Eyck J, Haak MC, van Pampus MG, Bruinse HW, Mol BWJ. Pessaries in multiple pregnancy as a prevention of preterm birth (the ProTwin Trial). *BMC Pregnancy and Childbirth* 2009, 9:44

RAVEL



Promovendus Drs. L. Freeman

Project leaders Dr JM Middeldorp, gynaecologist LUMC, Dr KWM Bloemenkamp, gynaecologist LUMC
Prof Dr A Dahan, anesthesiologist LUMC

ZonMw: 80-82310-97-11039

Nederlands Trial Register: NTR2551

Remifentanil patient controlled analgesia versus epidural analgesia during labor.

Objective

This study will investigate patient satisfaction and costs as main outcome. In this study patients receiving PCA remifentanil will titrate themselves to an acceptable level of pain relief by pressing a button (and receiving an analgesic bolus dose). It is expected that economical evaluation of both strategies will show a significant reduction in costs of this innovative strategy.

Study design

Randomized controlled multicentre trial

Study population

Women with a request for pain relief during labor between 32 and 42 weeks.

Methods

Women will be randomized before actual labor starts to receive either remifentanil PCA or epidural analgesia should they request pain relief during labor.

Outcome measures

This study will assess in women with a request for pain relief during labour the cost-effectiveness of RPCA as first choice treatment compared to EA. We will look at the following outcomes: costs, pain relief scores (pain-appreciation), patient satisfaction, pain scores (pain-intensity), maternal and neonatal side effects.

Power/data analysis

The initial analysis will be performed by intention to treat. We hypothesize that there is no difference in pain relief scores with the two sided test ($\alpha=0.05$, power $1-\beta=0.9$). In this non-inferiority design in each group 102 women have to be treated to exclude a potential clinically relevant difference of 10% (10 point scale, estimated SD 2.2). After correction for cross-over and non-compliance 568 patients are required. When only 50 percent of all women need actual treatment 1136 women have to be randomized.

Economic evaluation

The economic analysis will be performed from a short-term healthcare perspective. Anticipating on equality in pain relief scores the economic analysis will be a cost minimization analysis. For both strategies the cost of perinatal care for mother and child, starting at the onset of labor and ending ten days after delivery, will be registered and compared (without discounting).

Time schedule

36 months, including 27 months for inclusions (May 2011-October 2013)

TOSTI

TOSTI

Promovendus Drs. J. van de Ven, Máxima Medisch Centrum
Project leaders Prof. dr. S.G. Oei, gynecologist, Máxima MC
Prof. dr. B.W. Mol, gynaecologist AMC
ZonMw 80-82310-98-09040
Nederlands Trial Register: NTR1859

Training Obstetrische Spoed Teams Interventie (TOSTI)

Reducing errors in health care: cost-effectiveness of multidisciplinary team training in obstetric emergencies.

Objective

The aim of the study is to evaluate the cost-effectiveness of multidisciplinary team training in a medical simulation centre in the Netherlands to reduce the number of medical errors in obstetric emergency situations.

Study design

Multicentre randomised study with the centre as unit of analysis. Obstetric departments will be randomly assigned to receive multidisciplinary team training in a medical simulation centre or to a control arm.

Study population

Teaching and non-teaching hospitals in the Netherlands. We excluded hospitals which already have frequently multidisciplinary team training for its care workers. The intervention group will have multidisciplinary team training in a medical simulation centre. The control group will not have multidisciplinary team training.

Primary outcome

The number of obstetric complications throughout the first year after the intervention. Before the start of the project indicators will be developed to evaluate patient safety, teamwork and human factors. These indicators will be registered in a subgroup of the participating hospitals.

Power/data analysis

The analysis will be by intention-to-treat and stratified for teaching or non-teaching hospital. To show a reduction in perinatal asphyxia of 40% (from 1% to 0.6%) two groups of more than 8,000 patients are necessary.

Economic evaluation

The trial results will be incorporated in a cost-effectiveness analysis to compare the costs and effects of multidisciplinary team training in a medical simulation centre (experimental strategy) versus no such training (reference strategy).

Time schedule

Total study time 36 months. 9 months to develop indicators to evaluate patient safety, teamwork and human factors and schedule team trainings. 6 months team training in medical simulation centre. 12 months follow-up. 9 months analysis and report.

Economic analysis: We will calculate the costs of obstetric complications and of the training program itself. If multidisciplinary team training appears to be effective a cost-effective analysis will be performed.

Duration of the project: 36 months

Publications: Multidisciplinary team training in a simulation setting for acute obstetric emergencies: a systematic review. Merien AE, van de Ven J, Mol BW, Houterman S, Oei SG. *Obstet Gynecol.* 2010 May;115(5):1021-31. <http://www.ncbi.nlm.nih.gov/pubmed/20410778>

Study protocol. TOSTI study: reducing errors in health care: cost-effectiveness of multidisciplinary team training in obstetric emergencies; a randomised controlled trial. Van de Ven J, Houterman S, Steinweg RAJQ, Scherpbier AJJA, Wijers W, Mol BWJ, Oei SG. *BioMed Central, Pregnancy and Childbirth* 2010;10:59.

TOTEM



Promovendus Drs. E.C. van der Wilk, gynecologist
ErasmusMC, Rotterdam

Project leaders Prof.dr. E.A.P. Steegers, gynecologist
ErasmusMC Rotterdam, Dr. J.J. Duvekot, gynecologist
ErasmusMC Rotterdam

Nederlands Trial Register:

Temporise or Terminate pregnancy in women with severe preeclampsia at 28-34 weeks

Objective

The TOTEM trial investigates the hypothesis that temporising treatment of women with early-onset, severe preeclampsia with a gestational age between 28-34 weeks does not improve infant outcome as compared to termination of pregnancy 48 hours after admission and administering corticosteroids for inducement of fetal maturity.

Study design

Multicentre randomized controlled clinical trial

Study population

All women with working knowledge of the Dutch language with severe preeclampsia, gestational age at inclusion of 27.6 and 33.5 weeks, singleton pregnancy, estimated fetal weight < 500 gram and no known major fetal congenital anomalies.

Intervention

After admission for severe preeclampsia, patients will be stabilised with antihypertensive medication and magnesium sulphate and administered corticosteroids for inducement of fetal maturity according to standard practice. After 24 hours, patients, who did not develop a major maternal complication or a fetal indication for delivery, will be randomised for either termination of pregnancy 48 hours after admission or for expectant management.

Outcome measures

The primary outcome is composite major neonatal morbidity and perinatal mortality.

The secondary long-term neonatal outcome is a Bailey-3 assessment at two years corrected age. The secondary short-term maternal outcome is the occurrence of major complications before and after delivery. The secondary long-term maternal outcome is persistent morbidity or death.

Cost analysis calculates direct health care costs of mother and infant until discharge.

Power/data analysis

The randomised trial in our study will be a non-inferiority effectiveness trial.

On the basis of results from a previous study 1130 women have to be randomised to assure with 80% power that the upper limit of the 95% two-sided CI for the difference in composite neonatal morbidity will be within a prespecified non-inferiority boundary of 5%.

Economic evaluation

We will calculate direct health care costs (Short-term: direct hospital treatment costs of mother and infant. Long-term: medical treatment costs during first two years after delivery, estimate of long term health costs based on Bayley assessment and infant health at 2 years, expressed in QALY's) and indirect costs. In case of an improvement of neonatal outcome in the temporising management group, the economic analysis will be a cost-effectiveness analysis. Long term outcomes will be evaluated using modelling.

Time schedule

Randomisation 24 - 36 months.

Triple P

Triple P

Promovendus vacancy

Project leaders Dr. M.C. Haak VUMC, Dr. E. Pajkrt
AMC, Prof. dr. B.W. Mol, AMC

ZonMw 50-501 10-96-530

Nederlands Trial Register: NTR 2078

Objective

To evaluate whether a screening program with cervical length measurement to find women at risk for a preterm delivery, is cost-effective (the Triple P screening study). Women with a short cervical length are asked to take part in a follow-up study (the Triple P treat study) that evaluates whether subsequent progesterone treatment is effective.

Study design

Multicenter cohort study (Triple P screening) with a subsequent randomised clinical trial (Triple P treat).

Study population

Women with a singleton pregnancy undergoing fetal assessment at 16-20 weeks will be screened for a short cervical length (the Triple P screening study). If at 22 weeks this finding can be reproduced, women with a cervical length shorter than 25 mm will be invited to participate in a randomised clinical trial (the Triple P treat study). Cervical length will be measured with 40,000 women, in order to include 1920 women in the randomised clinical trial.

Intervention

Women participating in the Triple P treat study receive either vaginal progesterone (200 mg each night) or placebo from 24 to 34 weeks of gestation.

Outcome measures

Primary outcome is bad neonatal outcome. Secondary outcome measures are delivery before 34 weeks, child health, growth and development at 2 years, time to delivery, preterm birth rate before 32 and 37 weeks, days of neonatal admission, maternal morbidity, and maternal admission for preterm labor and costs.

Power analysis

Assuming a decrease of the incidence of bad neonatal outcome from 5% to 2.5%, using a two sided test with an alpha of 0.05 and a beta of 0.8, 1,920 women (960 per arm) are needed in this study.

The Triple P screening study: As we expect that 10% of the women will have a cervix < 25 mm, and if we assume that 50% of the eligible women will participate, we need to screen almost 40,000 women in this study.

Time schedule

We will need a run-in period of six months for the study set up, and 24 months for inclusion. After inclusion of the last patient, 30 months (6 months pregnancy and 24 months for evaluating the child at age 2) are needed for follow-up data collection and report of results. The first report on the primary outcome is expected at three years after start of the study.

Time schedule

Start in 2010, duration 4 years.

TRUST



Promovendus Drs. C. Kowalik, AMC
Project leaders Dr. B.W. Mol, AMC
Nederlands Trial Register: NTR1676

The Randomised Uterine Septum Transection Trial

Background

It is recognized that the prevalence of the septate uterus is increased in women with recurrent miscarriage (Homer et al, Fertil Steril 2000).

At present the finding of a septate uterus in women with recurrent miscarriage is not an indication for surgical correction of the septum. It is questionable if septoplasty in women with recurrent miscarriage will improve their reproductive outcome.

Objective

This study will answer the question if surgical intervention (septoplasty) in women with recurrent miscarriage and a septate uterus will improve their reproductive outcome.

Study design

A multi centre randomised controlled trial.

Study population

68 women with two or more recurrent miscarriages before 20 weeks of gestational age with a septate uterus.

Intervention

Random allocation to hysteroscopic septoplasty or no intervention.

Outcome measures and analysis

Primary outcome is live birth rate in each treatment group.

Secondary outcomes are complications following septoplasty; uterine perforation, fluid overload, endometritis, clinical pregnancy and miscarriage. In a subsequent pregnancy, we will look at the prevalence of adversary pregnancy outcomes, placental abruption, premature delivery, uterine rupture, and mode of delivery (vaginal vs. caesarean section).

The analysis of the randomised clinical trial will be by intention to treat. The live birth rates in the intervention group and the control group will be compared. Relative risks and 95% confidence intervals will be calculated for the relevant outcome measures.

Publicaties

- Bloemenkamp KW, Duvekot JJ, Kwee A, Mol BW, van Pampus MG, van der Post JA, Scheepers HC, Willekes C, Wouters MG. Physicians and scientific research: slight decline of the numbers of physicians with a doctoral degree. *Ned Tijdschrift Geneeskunde* 2006; 150: 2116-7. Dutch. No abstract available.
- Bloemenkamp KW, Duvekot JJ, Kwee A, Mol BW, van Pampus MG, van der Post JA, Scheepers HC, Willekes C, Wouters MG. Het verloskundig onderzoek consortium. *Ned Tijdschrift Geneeskunde* 2007.
- Bijlenga D, Birnie E, Mol BW, van der Post JAM, Bonsel GJ. Preferentie voor de wijze van bevalling bij à terme risicozwangerschappen: een obstetrisch Health Technology Assessment (HTZ) preferentieonderzoek. *Nederlands Tijdschrift voor Obstetrie en Gynaecologie* 2006; 119; 31-32.
- Boers K, Scherjon S, DIGITAT projectgroep. DIGITAT: Dysproportionate Intra-uterine Growth Intervention Trial At Term. *Nederlands Tijdschrift voor Obstetrie en Gynaecologie* 2006; 119; 26-27.
- Koopmans C, van Pampus M, HYPITAT projectgroep. HYPITAT 'Hypertension and Pre-eclampsia Intervention Trial At Term' Inleiden of afwachten? *Nederlands Tijdschrift voor Obstetrie en Gynaecologie* 2006; 119; 28-29.
- Lim AC, Bruinse HW, AMPHIA projectgroep. Het voorkómen van vroeggeboorte bij meerlingen: de AMPHIA-studie. *Nederlands Tijdschrift voor Obstetrie en Gynaecologie* 2006; 119; 24-25.
- Westerhuis MEMH, Kwee A, STAN projectgroep. Intrapartum foetale bewaking: MBO of STAN? *Nederlands Tijdschrift voor Obstetrie en Gynaecologie* 2006; 119; 37-38.
- Willekes C. Prematuur gebroken vliezen na 34 weken: inleiden of niet? *Nederlands Tijdschrift voor Obstetrie en Gynaecologie* 2006; 119; 40-41.
- Wolf H, Bilardo K, Arabin B, Derks J, Duvekot H, Oepkes D, Visser G. TRUFFLE-studie (Trial of Umbilical and Fetal Flow in Europe). *NTOG* 2006; 119; 33-34.
- Westerhuis M, Porath M, Mol BW, Kwee A. A comparison of intrapartum automated fetal electrocardiography and conventional cardiotocography--a randomised controlled study. *BJOG*. 2006 Sep;113(9): 1103
- Bijlenga D, Birnie E, Mol BW, Bonsel GJ. When outcome is a balance: methods to measure combined utility for the choice between induction of labour and expectant management in mild risk pregnancy at term. *BMC Pregnancy Childbirth*. 2007;7:10.
- Lim AC, Bloemenkamp KW, Boer K, Duvekot JJ, Erwich JJ, Hasaart TH, Hummel P, Mol BW, Offermans JP, van Oirschot CM, Santema JG, Scheepers HC, Schöls WA, Vandenbussche FP, Wouters MG, Bruinse HW; AMPHIA study group. Progesterone for the prevention of preterm birth in women with multiple pregnancies: the AMPHIA trial. *BMC Pregnancy Childbirth*. 2007;7:7.
- Van der Ham DP, Nijhuis JG, Mol BW, van Beek JJ, Opmeer BC, Bijlenga D, Groenewout M, Arabin B, Bloemenkamp KW, van Wijngaarden WJ, Wouters MG, Pernet PJ, Porath MM, Molkenboer JF, Derks JB, Kars MM, Scheepers HC, Weinans MJ, Woiski MD, Wildschut HI, Willekes C. Induction of labour versus expectant management in women with preterm

prelabour rupture of membranes between 34 and 37 weeks (the PPROMEXIL-trial). *BMC Pregnancy Childbirth*. 2007;7:11.

- Boers KE, Bijlenga D, Mol BW, LeCessie S, Birnie E, van Pampus MG, Stigter RH, Bloemenkamp KW, van Meir CA, van der Post JA, Bekedam DJ, Ribbert LS, Drogtróp AP, van der Salm PC, Huisjes AJ, Willekes C, Roumen FJ, Scheepers HC, de Boer K, Duvekot JJ, Thornton JG, Scherjon SA. Disproportionate Intrauterine Growth Intervention Trial At Term: DIGITAT. *BMC Pregnancy Childbirth*. 2007;7:12.
- Westerhuis ME, Moons KG, van Beek E, Bijvoet SM, Drogtróp AP, van Geijn HP, van Lith JM, Mol BW, Nijhuis JG, Oei SG, Porath MM, Rijnders RJ, Schuitemaker NW, van der Tweel I, Visser GH, Willekes C, Kwee A. A randomised clinical trial on cardiotocography plus fetal blood sampling versus cardiotocography plus ST-analysis of the fetal electrocardiogram (STAN) for intrapartum monitoring. *BMC Pregnancy Childbirth*. 2007 ;7:13.
- Koopmans CM, Bijlenga D, Aarnoudse JG, van Beek E, Bekedam DJ, van den Berg PP, Burggraaff JM, Birnie E, Bloemenkamp KW, Drogtróp AP, Franx A, de Groot CJ, Huisjes AJ, Kwee A, le Cessie S, van Loon AJ, Mol BW, van der Post JA, Roumen FJ, Scheepers HC, Spaanderman ME, Stigter RH, Willekes C, van Pampus MG. Induction of labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the HYPITAT trial. *BMC Pregnancy Childbirth*. 2007 ;7:14.
- Van der Ham DP, van de Laar R, Mol BW, Willekes C. Use of C-reactive protein as a predictor of chorioamnionitis in preterm prelabour rupture of the membranes: a systematic review. *BJOG*. 2008 ;115:127;
- Langenveld J, Mol BW, van der Post JA. Substandard care in maternal mortality due to hypertensive disease in pregnancy in the Netherlands. *BJOG*. 2008 Sep;115(10):1322-3
- Mol F, Strandell A, Jurkovic D, Yalcinkaya T, Verhoeve HR, Koks CA, van der Linden PJ, Graziosi GC, Thurkow AL, Hoek A, Hogström L, Klinte I, Nilsson K, van Mello NM, Ankum WM, van der Veen F, Mol BW, Hajenius PJ; European Surgery in Ectopic Pregnancy study group. The ESEP study: salpingostomy versus salpingectomy for tubal ectopic pregnancy; the impact on future fertility: a randomised controlled trial. *BMC Womens Health*. 2008 Jun 26;8:11.
- Westerhuis ME, van Horen E, Kwee A, van der Tweel I, Visser GH, Moons KG. Inter- and intra-observer agreement of intrapartum ST analysis of the fetal electrocardiogram in women monitored by STAN. *BJOG*. 2009 Mar;116(4):545-51
- Adverse drug reactions tot tocolytic treatment for preterm labour: a prospective cohort study. de Heus R, Mol BW, Erwich JJ, van Geijn HP, Gyselaers WJ, Hanssens M, Härmark L, van Holsbeke CD, Duvekot JJ, Schobben FF, Wolf H, Visser GH. *BMJ*. 2009 Mar 5;338:b744
- Michelle E.M.H. Westerhuis, Sanne M. Strasser, Karel G.M. Moons, Ben Willem J. Mol, Gerard H.A. Visser, Anneke Kwee. Intrapartum foetale bewaking: van stethoscoop naar ST-analyse van het electrocardiogram Geaccepteerd door Ned Tijdschrift voor Geneeskunde (NTvG)
- Corine M Koopmans, Ben WJ Mol, Henk Groen, Sylvia Vijgen, Denise Bijlenga, Jan G Aarnoudse, Dick J Bekedam, Paul P van den Berg, Karin de Boer, Jan M Burggraaff, Kitty WM Bloemenkamp, Addy P Drogtróp, Arie Franx, Christianne JM de Groot, Anjoke JM Huisjes, Anneke Kwee, Aren J van Loon, Annemiek Lub, Dimitri NM Papatsonis, Joris AM van der Post, Frans JME Roumen, Hubertina CJ Scheepers, Christine Willekes, Maria G van Pampus. Induction of labour versus expectant monitoring for gestational hypertension and preeclampsia after 36 weeks: The HYPITAT trial. *Lancet* 2009,3.

- Custers IM, Flierman PA, Maas P, Cox T, Van Dessel TJHM, Gerards MH, Mochtar MH, Janssen CAH, Van der Veen F, Mol BWJ. Immobilisation versus immediate mobilisation after intrauterine insemination: a randomised controlled trial. *BMJ* 2009;339.
- Hegeman MA, Bekedam DJ, Bloemenkamp KWM, Kwee A, Papatsonis DNM, van der Post JAM, Lim AC, Scheepers HCJ, Willekes C, Duvekot JJ, Spaanderman M, Porath M, van Eyck J, Haak MC, van Pampus MG, Bruinse HW, Mol BWJ. Pessaries in multiple pregnancy as a prevention of preterm birth (the ProTwin Trial). *BMC Pregnancy and Childbirth* 2009, 9:44
- Van Leijsen SA, Kluivers KB, Mol BW, Broekhuis SR, Milani FL, van der Vaart CH, Roovers JP, Bongers MY, den Boon J, Spaans WA, de Leeuw JW, Dietz V, Kleinjan JH, Brölmann HA, Roos EJ, Schaafstra J, Heesakkers JP, Vierhout ME. Protocol for the value of urodynamics prior to stress incontinence surgery (VUSIS) study: a multicenter randomized controlled trial to assess the cost effectiveness of urodynamics in women with symptoms of stress urinary incontinence in whom surgical treatment is considered. *BMC Womens Health*. 2009 Jul 21;9:22.
- Labrie J, van der Graaf Y, Buskens E, Tiersma SE, van der Vaart HC. Protocol for Physiotherapy Or TVT Randomised Efficacy Trial (PORTRET): a multicenter randomised controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. *BMC Womens Health*. 2009 Sep 1;9:24.
- Vis JY, Wilms FF, Oudijk MA, Porath MM, Scheepers HC, et al. Cost-effectiveness of fibronectin testing in a triage in women with threatened preterm labor: alleviation of pregnancy outcome by suspending tocolysis in early labor (APOSTEL-I trial). *BMC Pregnancy Childbirth*. 2009;9:38
- Koopmans, CM, Mol BW, van der Post JA, van Pampus MG for the HYPITAT study Group. HYPITAT and the Fallacy of pregnancy interruption. *Lancet*. 2010 Jan 9;375(9709):119-120
- Kowalik CR, Mol BW, Veersema S, Goddijn M, Critical appraisal regarding the effect on reproductive outcome of hysteroscopic metroplasty in patients with recurrent miscarriage. *Arch Gynecol Obstet*. 2010 Apr 1
- Woiski MD, Hermens RPMG, Middeldorp JM, Kremer JA, Marcus MA, Wouters MGAJ, Grol RP, Lotgering FK, Scheepers HCJ. Haemorrhagia post partum; an implementation study on the evidence-based guideline of the Dutch Society of Obstetrics and Gynaecology (NVOG) and the MOET (Managing Obstetric Emergencies and Trauma-course) instructions; the Fluxim study. *BMC Pregnancy Childbirth* 2010 Jan, 10:15.
- Woiski MD, Scheepers HCJ, Hermens RPMG. Hoe verbeteren wij de zorg omtrent Haemorrhagia post partum in Nederland. *Nederlands Tijdschrift voor Obstetrie & Gynaecologie*, vol. 123:38-39, februari 2010. Ingezonden brief.
- Babette W Prick et al. Well being of Obstetric patients on Minimal Blood transfusions (WOMB trial). *BMC Pregnancy and Childbirth* 2010, 10:33
- Stijn van Teeffelen , David van der Ham , Swan Oei , Martina Porath , Christine Willekes , Ben Mol. The accuracy of clinical parameters in the prediction of perinatal pulmonary hypoplasia secondary to midtrimester prelabour rupture of fetal membranes: a meta-analysis. In: *Eur J Obstet Gynecol Reprod Biol*. 2010 Jan;148(1):3-12. Epub . Review

- Hermes W, Franx A, van Pampus MG, Bloemenkamp KW, van der Post JA, Porath M, Ponjee G, Tamsma JT, Mol BW, de Groot CJ. 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study. *BMC Pregnancy Childbirth*. 2010 Jun 1;10:28
- Mallory D. Woiski, MD (Presenter), Hubertina C. Scheepers, Fred K. Lotgering, Richard Grol, Rosella P. Hermens. Development of guideline-based quality indicators for post partum hemorrhage (PPH) to improve quality of care (abstract) *Otolaryngology-Head and Neck Surgery* : Volume 143 Number 1S1, July 2010
- Bijlenga D, Birnie B, Bonsel GJ. Eliciting Willingness to Pay in obstetrics: Comparing a direct and an indirect valuation method for complex health outcomes. *Health Economics*, 2010.
- Verhoeven-Smeijers C, Bijlenga D, van Pampus MG, Mol BWJ. Onderzoek naar hypertensieve aandoeningen in de zwangerschap door het Verloskundig Consortium. *Inzicht* nr. 2, jaargang 15.
- Bakker JJH, Verhoeven CJM, Janssen PF, van Lith JM, van Oudgaarden ED, Bloemenkamp KWM, Papatsonis DNM, Mol BWJ, van der Post JAM. Outcomes after Internal versus External Tocodynamometry for Monitoring Labor. *N Engl J Med* 2010; 362:306-13.
- Kaandorp JJ, Benders MJ, et al. Antenatal allopurinol for reduction of birth asphyxia induced brain damage (ALLO-Trial); a randomized double blind placebo controlled multicenter study. *BMC Pregnancy and Childbirth* 2010, 10:8.
- C.Roos, L.Scheepers, K.Bloemenkamp, A.Bolte, J.Cornette, J.Derks, H.Duvekot, J.van Eyck, J.Kok, A.Kwee, A.Merién, B.Opmeer, M.van Pampus, D.Papatsonis, M.Porath, J.van der Post, S.Scherjon, K.Sollie, M.Spaanderman, S.Vijgen, C.Willekes, B.W.Mol, F.Lotgering. Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour. *BMC Pregnancy and Childbirth Study Protocol*, 9:42
- Mutsaerts MA, Groen H, Bogt Ter NC, Bolster JH, Land J, Bemelmans W, Kuchenbecker WK, Hompes PG, Macklon NS, Stolk RP, van der Veen F, Maas J, Klijn NF, Kaaijk EM, Oosterhuis GJ, Bouckaert PX, Schierbeek JM, van Kasteren YM, Nap AW, Broekmans FJ, Brinkhuis EA, Koks CA, Burggraaff JM, Blankhart AS, Perquin DA, Gerards MH, Mulder RJ, Gondrie ET, Mol BW, Hoek A. The LIFESTYLE study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. A randomised controlled trial. *BMC Womens Health*. 2010 Jun 25;10(1):22
- Langenveld J, Jansen S, van der Post JA, Wolf H, Mol BW, Ganzevoort W. Recurrence risk of a delivery before 34 weeks of pregnancy due to a severe hypertensive disorder: a systematic review. *Am J of Perinat*. 2010 Aug; 27 (7): 565-71.
- Ectopic pregnancy and pelvic inflammatory disease: a renewed epidemic? *Mol F, van Mello NM, Mol BW, van der Veen F, Ankum WM, Hajenius PJ. Eur J Obstet Gynecol Reprod Biol*. 2010 Aug;151(2):163-7
- Conservative management of tubal ectopic pregnancy. *van Mello NM, Mol F, Mol BW, Hajenius PJ. Best Pract Res Clin Obstet Gynaecol*. 2009 Aug;23(4):509-18
- Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Barnhart K, van Mello NM, Bourne T, Kirk E, Van Calster B, Bottomley C, Chung K, Condous G, Goldstein S, Hajenius PJ, Mol BW, Molinaro T, O'Flynn O'Brien KL, Husicka R, Sammel M, Timmerman D. Fertil Steril*. 2010 Oct 12

- Labour and neonatal outcome in small for gestational age babies delivered beyond 36+0 weeks: a retrospective cohort study. Boers KE, van der Post JA, Mol BW, van Lith JM, Scherjon SA. *J Pregnancy*. 2011;2011:293516. Epub 2010 Dec 15. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3066629/?tool=pubmed>
- Salpingotomy or salpingectomy in tubal ectopic pregnancy: what do women prefer? van Mello NM, Mol F, Opmeer BC, de Bekker-Grob EW, Essink-Bot ML, Ankum WM, Mol BW, van der Veen F, Hajenius PJ. *Reprod Biomed Online*. 2010 Nov;21 (5):687-93. Epub 2010 Jun 30
- Guideline adherence in ectopic pregnancy management. Mol F, van den Boogaard E, van Mello NM, van der Veen F, Mol BW, Ankum WM, van Zonneveld P, Dijkman AB, Verhoeve HR, Mozes A, Goddijn M, Hajenius PJ. *Hum Reprod*. 2010 Dec 2. [Epub ahead of print]
- Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT). Boers KE, Vijgen SM, Bijlenga D, van der Post JA, Bekedam DJ, Kwee A, van der Salm PC, van Pampus MG, Spaanderman ME, de Boer K, Duvetkot JJ, Bremer HA, Hasaart TH, Delemarre FM, Bloemenkamp KW, van Meir CA, Willekes C, Wijnen EJ, Rijken M, le Cessie S, Roumen FJ, Thornton JG, van Lith JM, Mol BW, Scherjon SA; DIGITAT study group. *BMJ*. 2010 Dec 21;341:c7087. doi: 10.1136/bmj.c7087 <http://www.bmj.com/content/341/bmj.c7087.full.html>
- Bijlenga D, Boers KE, Birnie E, Mol BW, Vijgen SCM, van der Post JAM, De Groot CJ, Rijnders RJP, Pernet PJ, Roumen FJ, Stigter RH, Delemarre FMC, Bremer HA, Porath M, Scherjon SA, Bonsel GJ. Maternal health-related quality of life after induction of labor or expectant monitoring in pregnancy complicated by intrauterine growth retardation beyond 36 weeks. *Quality of Life Research*, 2011
- Langenveld J, Buttinger A, van der Post JA, Wolf H, Mol BW, Ganzevoort W. Recurrence risk and prediction of a delivery under 34 weeks after a history of a severe hypertensive disorder. *BJOG* 2011 Feb 4
- Maternal health-related quality of life after induction of labor or expectant monitoring in pregnancy complicated by intrauterine growth retardation beyond 36 weeks. Bijlenga D, Boers KE, Birnie E, Mol BW, Vijgen SC, Van der Post JA, De Groot CJ, Rijnders RJ, Pernet PJ, Roumen FJ, Stigter RH, Delemarre FM, Bremer HA, Porath M, Scherjon SA, Bonsel GJ. *Qual Life Res*. 2011 Apr 6. [Epub ahead of print]
- van Kuijk SM, Nijdam ME, Janssen KJ, Sep SJ, Peeters LL, Delahaije DH, Spaanderman M, Bruinse HW, Franx A, Bots ML, Langenveld J, van der Post J, van Rijn BB, Smits L. A Model for Preconceptional Prediction of Recurrent Early-Onset Preeclampsia: Derivation and Internal Validation. *Reprod Sci*. 2011 Jun 14
- Koopmans CM, Zwart JJ, Groen H, Bloemenkamp KWM, Mol BWJ, van Pampus MG, van Roosmalen J. Risk indicators for eclampsia in women with gestational hypertension or mild preeclampsia at term: a case-control study. *Hypertens Pregnancy*. 2010 Sep 7 [Epub ahead of print]
- Vijgen SMC, Koopmans CM, Opmeer BC, Groen H, Bijlenga D, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KWM, Drogdroop AP, Franx A, de Groot CJM, Huisjes AJM, Kwee A, van Loon AJ, Lub A, Papatsonis DNM, van der Post JAM, Roumen FJME, Scheepers HCJ, Stigter RH, Willekes C, Mol BWJ, van Pampus MG. An economic analysis of induction of labor and expectant monitoring in women with gestational hypertension or preeclampsia at term (HYPITAT trial). *BJOG*. 2010 Sep 14 [Epub ahead of print].

- Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ, van den Berg PP, de Boer K, Burggraaff JM, Bloemenkamp KWM, Drogtrop AP, Franx A, de Groot CJM, Huisjes AJM, Kwee A, van Loon AJ, Lub A, Papatsonis DNM, van der Post JAM, Roumen FJME, Scheepers HCJ, Willekes C, Mol BWJ, van Pampus MG. Liever inleiden dan afwachten bij atermen zwangerschapshypertensie en milde preëclampsie: de HYPITAT studie. *NTvG*, 2010 (154), nummer 22
- Westerhuis MEMH, Visser GHA, Moons KGM, et al. Cardiotocography Plus ST Analysis of Fetal Electrocardiogram Compared With Cardiotocography Only for Intrapartum Monitoring: A Randomized Controlled Trial. *Obstet Gynecol* 2010;115:1173-80
- Van Kuijk SM, Sep SJ, Nelemans PJ, Smits LJ. How long do preconception risk prediction models hold? Influence of selective fertility on model performance. *Paediatr Perinat Epidemiol*. 2010 Nov;24(6):602-7
- Delahaije DH, van Kuijk SM, Dirksen CD, Sep SJ, Peeters LL, Spaanderman ME, Bruinse HW, de Wit-Zuurendonk LD, van der Post JA, Duvekot JJ, van Eyck J, van Pampus MG, van der Hoeven MA, Smits LJ. Cost-effectiveness of recurrence risk guided care versus care as usual in women who suffered from early-onset preeclampsia including HELLP syndrome in their previous pregnancy (the PreCare study). *BMC Pregnancy Childbirth*. 2010 Oct 11;10:60
- Multidisciplinary team training in a simulation setting for acute obstetric emergencies: a systematic review. Merien AE, van de Ven J, Mol BW, Houterman S, Oei SG. *Obstet Gynecol*. 2010 May;115(5):1021-31. <http://www.ncbi.nlm.nih.gov/pubmed/20410778>
- Study protocol. TOSTI study: reducing errors in health care: cost-effectiveness of multidisciplinary team training in obstetric emergencies; a randomised controlled trial. Van de Ven J, Houterman S, Steinweg RAJQ, Scherpbier AJJA, Wijers W, Mol BWJ, Oei SG. *BioMed Central, Pregnancy and Childbirth* 2010;10:59. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964561/pdf/1471-2393-10-59.pdf>
- Verhoeven. C, de Miranda, E, De Triple P studie. *TvV*. July-august 2010 31-31. Article *TvV* July/august 2010
- Vlemmix F, Rosman AN, Fleuren MA, Rijnders ME, Beuckens A, Haak MC et al. Implementation of the external cephalic version in breech delivery. Dutch national implementation study of external cephalic version. *BMC Pregnancy Childbirth* 2010; 10:20
- Lim AC, Mol BWJ, Bruinse HW. *Progesteron ter preventie van vroeggeboorte: de stand van zaken*. *Nederlands Tijdschrift voor Geneeskunde*. 2010;154:A1730
- David P van der Ham, Marjo M van Melick, Luc Smits, Jan G Nijhuis, Carl P Weiner, J (Hans) J van Beek, Ben Willem J Mol, Christine Willekes. Methods for the diagnosis of rupture of the fetal membranes in equivocal cases: a systematic review. In: *Eur J Obstet Gynecol Reprod Biol*. 2011 Apr 7. [Epub ahead of print]
- Westerhuis MEMH, Visser GHA, Moons KGM, Zuithoff NPA, Mol BWJ, Kwee A. Letter to the editor to: Cardiotocography plus ST analysis of fetal electrocardiogram compared with cardiotocography only for intrapartum monitoring: a randomized controlled trial. *Obstet Gynecol* 2011; 117 (in press)

Voordrachten

- Van der Post JA. Start van het consortium verloskundig onderzoek. Gynaecongres Nijmegen 2006
- Kwee A, Bruinse HW, Wolf H. Nieuwe studies binnen het consortium. Gynaecongres Nijmegen 2006
- Scherjon S en Van Pampus MG. De Digitat en Hypitat studie. Gynaecongres Nijmegen 2006
- Mol BW. Het consortium verloskundig onderzoek: (hoe) gaan we verder? Gynaecongres Nijmegen 2006
- Mol BW, Lim AC, Bruinse HW, voor de AMHIA projectgroep. Progesteron ter profylaxe van vroeggeboorte. Doelen Congres Infertilititeit, Gynaecologie en Obstetrie. April 2007.
- Westerhuis M, Kwee A, voor de STAN projectgroep. Foetale bewaking anno 2007. Doelen Congres Infertilititeit, Gynaecologie en Obstetrie. April 2007.
- Mol BW, Lim AC, Bruinse HW, voor de AMHIA projectgroep. Progesteron ter profylaxe van vroeggeboorte. Doelen Congres Infertilititeit, Gynaecologie en Obstetrie. April 2007.
- Lim AC, Bruinse HW, Boer K, Mol BW. Progesteron ter preventie van vroeggeboorte. Werkgroepvergadering Perinatologie en Maternale Ziekten, Domus Medica, Utrecht, 30 november 2007.
- CM Koopmans, BWJ Mol, H Groen, S Vijgen, D Bijlenga, PP van den Berg, AJ van Loon, JM Burggraaff, KWM Bloemenkamp, JAM van den Post, DJ Bekedam, A Lub, HCJ Scheepers, K de Boer, AP Drogtróp, A Franx, CJM de Groot, A Kwee, AJM Huisjes, C Willekes, FJME Roumen, D Papatsonis, MG van Pampus. Hypertension and Preeclampsia Intervention Trial At Term: de HYPITAT studie, presentatie Hypitat symposium Deventer 9 mei 2008
- Koopmans CM, BWJ Mol, H Groen, S Vijgen, D Bijlenga, PP van den Berg, AJ van Loon, JM Burggraaff, KWM Bloemenkamp, JAM van den Post, DJ Bekedam, A Lub, HCJ Scheepers, K de Boer, AP Drogtróp, A Franx, CJM de Groot, A Kwee, AJM Huisjes, C Willekes, FJME Roumen, D Papatsonis, MG van Pampus. Hypertension and Preeclampsia Intervention Trial At Term: de HYPITAT studie, presentatie . NVOG congres te Haarlem:
- Koopmans CM, Van den Berg PP, Mol BWJ, Groen H, Willekes C, Kwee A, Bloemenkamp KWM, Van den Post JAM, Scheepers HCJ and Van Pampus MG. Pregnancy-induced hypertension and preeclampsia after 36 weeks: induction of labour versus expectant monitoring: The HYPITAT trial. 16th World Congress International Society for the Study of Hypertension in Pregnancy. Washington 21-24 september 2008: Zuspan award.
- van der Tuuk K, Koopmans CM, Groen H, Rijnders RJP, van Beek JJ, Porath M, van den Berg PP, van der Salm PCM, Mol BWJ, van Pampus MG. Prediction of deterioration of the clinical condition in women with pre-eclampsia or pregnancy induced hypertension at term. 16th World Congress International Society for the Study of Hypertension in Pregnancy. Washington 21-24 september 2008:
- Bijlenga D, Birnie E, Mol BWJ, Bekedam DJ, de Boer K, Drogtróp AP, Franx A, de Groot CJM, van Pampus MG, Bonsel GJ. Health-related quality of life after induction of labor or expectant management in pregnancy-induced hypertension and preeclampsia at term. Poster presentation. 16th World Congress International Society for the Study of Hypertension in Pregnancy. Washington 2008
- Vijgen SMC, Opmeer BC, Mol BWJ, Bijlenga D, Burggraaf JM, Van Loon AJ, Huisjes AJM, Roumen FJME, Papatsonis DNM, and Van Pampus MG for the HYPITAT study group. An economic analysis of induction of labor and expectant management in women with pregnancy-induced hypertension or pre-eclampsia at term. 16th World Congress International Society for the Study of Hypertension in Pregnancy. September 2008. Washington, DC. Poster Presentation.

- Vijgen SMC, Opmeer BC, Mol BWJ, Bijlenga D, Burggraaf JM, Van Loon AJ, Huisjes AJM, Roumen FJME, Papatsonis DNM, and Van Pampus MG for the HYPITAT study group. An economic analysis of induction of labor and expectant management in women with pregnancy-induced hypertension or pre-eclampsia at term. 11th Annual European Meeting International Society of Pharmacoeconomics and Outcomes Research. November 2008. Athens, Greece. Poster Presentation.
- Koopmans CM voor de de Hypitat study groep. Pregnancy-induced hypertension and preeclampsia after 36 weeks: induction of labour versus expectant monitoring: The HYPITAT trial. Nedwep: November 2008:
- Westerhuis MEMH, Visser GHA, Moons KGM, Beek van E, Bijvoet SM, Dessel van HJHM, Drogdrop AP, Geijn van HP, Graziosi GCM, Groenendaal F, Lith van JMM, Mol BWJ, Nijhuis JG, Oei SG, Oosterbaan HP, Porath MM, Rijnders RJP, Schuitemaker NWE, Sopacua LM, Tweel van der I, Wijnberger LDE, Willekes C, Kwee A. Foetale bewaking durante partu: resultaten van de Nederlandse STAN-trial. *Gynaecongres Arnhem, 14 november 2008*
- Kwee A, namens STAN-projectgroep. Foetale bewaking durante partu: resultaten van de Nederlandse STAN-trial. Doelencongres, 6 maart 2009
- Vijgen SMC on behalf of the STAN study group. Cost effectiveness of cardiotocography plus ST-analysis of the fetal electrocardiogram compared to cardiotocography plus fetal blood sampling. A poster presentation at the congress of the Society of Gynaecologic Investigation 2009 (Glasgow, March).
- Westerhuis MEMH, Visser GHA, Moons KGM, Beek van E, Bijvoet SM, Dessel van HJHM, Drogdrop AP, Geijn van HP, Graziosi GCM, Groenendaal F, Lith van JMM, Mol BWJ, Nijhuis JG, Oei SG, Oosterbaan HP, Porath MM, Rijnders RJP, Schuitemaker NWE, Sopacua LM, Tweel van der I, Wijnberger LDE, Willekes C, Kwee A. Cardiotocography plus ST-analysis of the fetal electrocardiogram versus cardiotocography plus fetal blood sampling: preliminary results of a Dutch randomised clinical trial *SGI Glasgow, 18 maart 2009 (Wyeth Presenter's Award)*
- Kwee A, namens STAN-projectgroep. Foetale bewaking durante partu: resultaten van de Nederlandse STAN-trial. GEM congres Putten, 27 maart 2009
- Van Pampus M, namens HYPITAT projectgroep: resultaten van de HYPITAT trial. GEM congres Putten, 27 maart 2009
- Mol, F: EUG stand van zaken. Jaarvergadering werkgroep Gynaecologische Endoscopie (WGE), april 2009.
- Van Pampus M. Het Verloskundig Consortium, presentatie op de chirurgen dagen 2009 Veldhoven, mei 2009.
- Mol, F: Salpingotomy versus salpingectomy, what do women prefer? Oral presentation ESHRA Atlanta, oktober 2009
- K van der Tuuk, MG van Pampus, CM Koopmans, JG Aarnoudse, PP van den Bert, JJ van Beek, FJA Copraij, G Kleiverda, M Porath, RJP Rijnders, PCM van der Salm, LP Morssink, RH Stigter, BWJ Mol, H Groen. Prediction of caesarean section in women with gestational hypertension or preeclampsia at term: induction of labour versus expectant monitoring. *AJOG*; vol 201; December 2009 nr 6; abstract 157 (posterpresentation SMFM Chicago 2010)
- CM Koopmans, JJ Zwart, H Groen, KWM Bloemenkamp, BWJ Mol, MG van Pampus, J van Roosmalen. Risk indicators for eclampsia in women with gestational hypertension or mild preeclampsia at term: a case-control study. *AJOG*; vol 201; December 2009 nr 6; abstract 778 (posterpresentation SMFM Chicago 2010)
- SM Vijgen, K Boers, BC Opmeer, D Bijlenga, C Willekes, KW Bloemenkamp, M Spaanderman, JA van der Post, DJ Bekedam, A Kwee, PC van der Salm, MG van Pampus, K de Boer, HJ Duvekot, HA Bremer, TH Hasaart, FM Delemarre, CA van Meir, EJ Wijnen, M Rijken, S Le Cessie, FJ Roumen, JM van Lith, BW Mol, SA Scherjon. An economic

analysis comparing induction of labour and expectant management for intrauterine growth restriction at term (Digitat Trial) AJOG; vol 201; December 2009 nr 6; abstract 98 (posterpresentation SMFM Chicago 2010)

- J Kaandorp for the ALLO-trial studygroup Presentatie Digitat Symposium 27-05-2009
- Vis JY, Mol BW. APOSTEL 1 trial. European Surgical User Group Meeting. October 2008. Brussels, Belgium. Oral Presentation.
- Neonatal outcome of pregnancies complicated by PPROM between 34 and 37 weeks of gestation. David P van der Ham, Jantien van der Heijden, Anita CJ Ravelli, Jan G Nijhuis, A (Twan) Mulder, J (Hans) J van Beek, Ben Willem J Mol, Christine Willekes. 30th Annual Meeting of the Society of Maternal Fetal Medicine – Chicago, USA
- Vis JY, for the APOSTEL study group. APOSTEL-1 study. Spinoza Chair Symposium Prenatal Screening in the Netherlands. March 2010. Amsterdam, The Netherlands. Oral presentation.
- Vis JY, for the APOSTEL study group. APOSTEL-1 study. Regionale Onderwijsbijeenkomst Obstetrie en Gynaecologie Cluster Rotterdam. March 2010. Amsterdam, The Netherlands. Oral presentation.
- Oral presentation September 2008 16th World Congress ISSHP, Washington. Langenveld et al. Outcome of subsequent pregnancy of women with severe hypertensive disorders before 34 weeks of gestation in the first (index) pregnancy.
- Westerhuis MEMH for the STAN study group. Intrapartum fetal monitoring: identification of cases with adverse neonatal outcome. SMFM annual meeting February 2010. Chicago, USA. Oral presentation
- Westerhuis MEMH for the STAN study group. Prediction of neonatalmetabolic acidosis in women with a term singleton fetus in cephalic position. SMFM annual meeting February 2010. Chicago, USA. Poster presentation.
- Becker JH for the STAN study group. The value of fetal blood sampling in addition to ST-analysis of the fetal electrocardiogram: results from the Dutch STAN trial. SMFM annual meeting February 2010. Chicago, USA. Poster presentation
- Vijgen SMC for the STAN study group. Cost-effectivenessof cardiocography plus ST-analysis of the fetal electrocardiogram compared to cardiocography only. SMFM annual meeting February 2010. Chicago, USA. Poster presentation
- Lim AC for the AMPHIA study group. Is second trimester cervical length a predictor for an effect of 17-alpha hydroxyprogesterone caproate on neonatal morbidity in multiple pregnancies? Preliminary results from the AMPHIA-trial. Society for Gynecologic Investigation Annual Meeting, Glasgow. Maart 2010. Poster presentation
- Kwee A. De plaats van het MBO en navelstrengbloedgassen op de verloskamer. Bloedgassensymposium. Maart 2010, Utrecht, The Netherlands. Oral presentation
- Lim AC, namens de AMPHIA projectgroep. Voorlopige resultaten van de AMPHIA-trial. Pijlerdag Koepel Foeto-Maternale Geneeskunde NVOG, Nieuwegein. April 2010. Oral presentation
- Kwee A. Foetale Bewaking anno 2010. De STAN(d) van zaken. Siemens symposium Zuurbasediagnostiek rondom de geboorte. Mei 2010, Zeist, The Netherlands. Oral presentation
- Lim AC, Hummel P, Papatsonis D, Hasaart THM, van Oirschot CM, van Eijck J, Porath MM, Kleiverda G, de Graaf IM, van Ginkel AA, Mol BWJ, Bruinse HW. The effect of 17-alpha hydroxyprogesterone caporate on cervical length in multiple pregnancies. Society for Gynecologic Investigation Annual Meeting, Orlando. Maart 2010 / Gynaecongres, 3-4 juni 2010. Poster presentation

- Oral presentation Oktober 2010 17th World Congress ISSHP, Melbourne. Langenveld et al. Neonatal outcome of pregnancies complicated by hypertensive disorders between 34 and 37 weeks of gestation. Young investigator travel award.
- van Kuijk SM, Nijdam ME, Jansen K, Sep S, Smits L, et al. A Preconception Prediction Model for the Identification of Women at Low Risk for Recurrence of Early-Onset Preeclampsia or HELLP. Aspects of hypertensive disorders in pregnancy, Mini Symposium. AMC, Amsterdam. 31 January 2010. Oral presentation.
- van Kuijk SM, Nijdam ME, Jansen K, Sep S, Smits L, et al. A Preconception Prediction Model for the Identification of Women at Low Risk for Recurrence of Early-Onset Preeclampsia or HELLP. WEON, Nijmegen. 11 June 2010. Oral presentation.
- Lim AC. Prevention strategies for premature delivery with multiple pregnancy? Facts and fiction. International Congress on Twin Studies, Seoul. Juni 2010. Oral presentation.
- Lim AC, namens de AMPHIA projectgroep. Is cervixlengte in het tweede trimester een voorspeller voor het effect van 17-alpha hydroxyprogesteron caproaat op neonatale morbiditeit in meerlingzwangerschappen? Resultaten van de AMPHIA-trial. Gynaecongres, Breda. Juni 2010. Oral presentation.
- van Kuijk SM, Sep S, Nelemans P, Smits S. How Long do Preconception Prediction Models Hold? influence of selective fertility on model performance. WEON, Nijmegen, 11 June 2010. Poster presentation
- Van de Ven J, for the TOSTI study group. Special interest group obstetrics. Team training in acute obstetrics. Congress Society in Europe for Simulation Applied to Medicine (SESAM). June 2010. Groningen, the Netherlands. Oral presentation
- Van de Ven J, for the TOSTI study group. Reducing errors in health care: cost-effectiveness of multidisciplinary team training in obstetric emergencies: the TOSTI trial. Congress Society in Europe for Simulation Applied to Medicine (SESAM). June 2010. Groningen, the Netherlands. Poster presentation
- Van de Ven, for the TOSTI study group. Onderwijsavond Maxima Medisch Centrum. Teamtraining in de acute verloskunde. May 2010. Veldhoven, the Netherlands. Oral presentation
- Van de Ven, for the TOSTI study group. OOR-ZON symposium Oefening baart kunst, interactieve sessie praktische toepassing van skillstrainingen in de opleiding tot medisch specialist. Teamtraining in acute verloskunde. April 2010. Maastricht, the Netherlands. Oral presentation
- Westerhuis MEMH. Intrapartum foetale bewaking. STAN versus CTG: een update. Refereeravond VU Medisch Centrum, april 2010, Amsterdam, The Netherlands. Oral presentation
- Antepartum predictie van neonatale sepsis bij vrouwen met PPROM tussen 34 en 37 weken. D.P. van der Ham, on behalf of the PPROMEXIL study Group. Gynaecongres, Sessie: In opleiding 1 – Breda
- Roos C, namens de APOSTEL II projectgroep: Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour. Gynaecongres, Breda, The Netherlands, June 4th 2010. Oral presentation
- Induction of Labor Versus Expectant Management in Women with Preterm Prelabor Rupture of Membranes between 34 and 37 Weeks - the PPROMEXIL trial -David P van der Ham on behalf of the PPROMEXIL trial Group. 57th Annual Scientific Meeting of the Society of Gynecological Investigation – Orlando, USA
- Westerhuis MEMH en Kwee A. De nederlandse STAN trial en secundaire analyses. BMA mini symposium, 16 september 2010, Utrecht, The Netherlands. Oral presentations
- Westerhuis MEMH. De nederlandse STAN trial. STAN minisymposium Universitair Ziekenhuis Antwerpen, 28 september 2010, Antwerpen, Belgium. Oral presentation

- Marta Jozwiak namens de PROBAAT studie groep. Prostaglandines of ballon voor inleiden van de baring a terme: de PROBAAT studie - voorlopige resultaten. Residents Research Day Leiden, September 2010
- Westerhuis MEMH. The Dutch STAN trial. Swedish conference on intrapartum fetal monitoring. 27 October 2010, Stockholm, Sweden. Oral presentation
- van Os M.A. for the Triple P study group, TripleP study. Spinoza chair april 2010 Prenatal screening in the netherlands AMC Amsterdam The netherlands, oral presentation. Presentation Triple P Spinoza chair 2010
- Roos C, namens de APOSTEL II projectgroep: Prediction of labour within 7 days in women admitted for threatened preterm labour. Gynaecongres, Arnhem, The Netherlands, November 11th 2010. Oral presentation.
- Marta Jozwiak namens de PROBAAT studie groep. PROBAAT studie: voorlopige resultaten. Gynaecongres Arnhem, November 2010. Oral presentation
- ISSHP Prediction neonatal complications (Abstract Oral ISSHP 2010 Melbourne)
- ISSHP Prediction postpartum hemorrhage (Abstract Oral ISSHP 2010 Melbourne)
- R. de Heus on behalf of the VET study group. Fetal Medicine foundation World Congress Rhodos. Maternal serious adverse events with the use of tocolytic drugs (poster presentation) 2010
- Hermes W, namens de HyRAS studie groep: *The Hypertension Risk Assessment Study (HyRAS)*, Wetenschapsmiddag MCH Westeinde, 8 December 2010. Oral presentatie
- Induction of Labour versus Expectant management in women with Preterm Prelabour Rupture of Membranes between 34 and 37 weeks (PPROMEXIL trial) D.P. van der Ham, on behalf of the PPRMEXIL study group. Dutch Society of Perinatal Medicine, Bronovo, the Hague
- Hermes W, on behalf of the HyRAS study group: *The Hypertension Risk Assessment Study (HyRAS)*, Wednesday 12 January 2011, HYPITAT symposium Groningen: Oral presentation
- Lim AC, Schuit E, on behalf of the AMPHIA project group. Mid-pregnancy cervical length as a predictor of preterm birth in multiple pregnancies. Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. Februari 2011. Poster presentation
- Lim AC, Schuit E, on behalf of the AMPHIA project group. Mid-pregnancy cervical length and the risk of cesarean delivery in multiple pregnancies. Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. Februari 2011. Poster presentation.
- Marta Jozwiak for the Probaat study Group. Induction of labor at term: a comparison of Foley catheter and prostaglandins. Society of Maternal Fetal Medicine 31st annual Meeting. San Fransisco, February 2011. Oral presentation
- Prediction of neonatal sepsis in women with PPRM between 34 and 37 weeks of gestational age. David P van der Ham on behalf of the PPRMEXIL study Group. 31th Annual Meeting of the Society of Maternal-Fetal Medicine – San Francisco, USA
- Does induction of labor in women with a positive GBS vaginal culture decrease the risk for neonatal sepsis in women with PPRM between 34 and 37 weeks? David P van der Ham on behalf of the PPRMEXIL study Group. 31th Annual Meeting of the Society of Maternal Fetal Medicine – San Francisco, USA
- SMFM 2011 Impact of Hypitat trial (*Abstract SMFM 2011 San Francisco*)
- Roos C, Spaanderman M, Bloemenkamp K, Bolte A, Cornette J, Duvetkot H, Van Eyck J, Kok J, Kwee A, Meriën A, Opmeer B, Oudijk M, Van Pampus M, Papatsonis D, Porath M, Scheepers L, Scherjon S, Schuit E, Sollie K, Vijgen S, Willekes C, Mol BW, Van der Post J, Lotgering F: Assessment of Perinatal Outcome with Sustained Tocolysis in Early Labour. Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. February 2011. Oral presentation.

- Vis J, Roos C, Van Straalen J, Bloemenkamp K, Bolte A, Cornette J, Duvekot H, Van Eyck J, Kok J, Kwee A, Meri n A, Opmeer B, Oudijk M, Van Pampus M, Papatsonis D, Porath M, Van der Post J, Scheepers L, Scherjon S, Schuit E, Sollie K, Spaanderman M, Willekes C, Lotgering F, Mol BW: Does fibronectin status influence the effectiveness of sustained tocolysis in women with threatened preterm labour? Society for Maternal-Fetal Medicine Annual Meeting, San Francisco. February 2011. Poster presentation.
- Posterpresentatie SMFM San Fransisco 2011. Neonatal morbidity in the DIGITAT RCT: Induction vs. Expectant monitoring in at term growth restriction. Kim E. Boers, Linda van Wyk, Saskia le Cessie, Sicco S. Scherjon, on behalf of DIGITAT study Group
- Hermes W, on behalf of the HyRAS study group: *The HyRAS study*. SMFM Congres San Francisco, Wednesday 9 February 2011: Oral presentation
- Hermes W, Franx A, de Bok F, Loix S, van der Hout E, ten Horn H, van Pampus M, Porath M, van der Post J, Bloemenkamp K, Mol BW, de Groot C: Hypertension 21/2 years after (near) term gestational hypertension or preeclampsia; The Hypertension Risk Assessment Study (HyRAS). SMFM, 12 February 2011. Poster presentation
- Visser S, Hermes W, Franx A, Koopmans C, van Pampus M, Mol B, de Groot C: Hypertension 6 weeks and 21/2 years after (near) term pregnancies complicated by hypertensive disorders. SGI, 19 March 2011. Poster presentation
- Hermes W, on behalf of the HyRAS study group: Classic Cardiovascular Risk Factors 2½ years after pregnancy complicated by hypertensive disease at term. 17 March 2011, SGI Miami: Oral presentation
- Presentatie Pijlerdag Koepel Foeto-Maternale Geneeskunde 13 april 2011. Wanneer is het voor iets te klein nog iets te vroeg, neonatale morbiditeit in de DIGITAT-RCT
- Marta Jozwiak namens de Probaat studie groep. PROBAAT studie: de resultaten. KNOV studiedag klinisch verloskundigen Utrecht, april 2011. Oral presentation
- Marta Jozwiak namens de PROBAAT studie groep. De wedergeboorte van de ballon. IGO-doelencongres Rotterdam, april 2011. Oral presentation
- Hermes W, Arie Franx, Clara Kolster, Femke de Bok, Stephanie Loix, Evelien van der Hout, Hilde ten Horn, Maria van Pampus, Martina Porath, Joris van der Post, Kitty Bloemenkamp, Ben Willem Mol, Christianne de Groot, namens HyRAS study group. Klassieke cardiovasculaire risicofactoren 21/2 jaar na een zwangerschap gecompliceerd door a terme (milde) preeclampsie of zwangerschapshypertensie: de HyRAS studie. Gynaecongres 19 mei 2011. Poster presentatie
- Marta Jozwiak, Katrien Oude Rengerink, Hans Doornbos, Addy Drogdrop, Christianne de Groot, Anjoke Huisjes, Gunilla Kleiverda, Jan Willem de Leeuw, Simone Lunshof, Claudia van Meir, Mari lle van Pampus, Pauline van der Salm, Nico Schuitemaker, Christine Willekes, Laura Zuurendonk, Ben Willem Mol, Kitty Bloemenkamp, namens de PROBAAT studie Projectgroep. Predictie van sectio caesarea bij vrouwen met een onrijpe cervix a terme. Gynaecongres Zwolle, mei 2011. Poster presentation
- Hermes W, Arie Franx, Clara Kolster, Femke de Bok, Stephanie Loix, Evelien van der Hout, Hilde ten Horn, Maria van Pampus, Martina Porath, Joris van der Post, Kitty Bloemenkamp, Ben Willem Mol, Christianne de Groot, namens HyRAS study group. Klassieke cardiovasculaire risicofactoren 21/2 jaar na een zwangerschap gecompliceerd door a terme (milde) preeclampsie of zwangerschapshypertensie: de HyRAS studie. Gynaecongres 20 mei 2011. Oral presentatie
- R. de Heus on behalf of the VET study group. Congres vroeggeboorte Utrecht Tocolyse: de stand van zaken. 2011

Adviesraden

Raad van Advies

Drs. C. Bos
Prof. dr. H. Kanhai (LUMC)
Dr. L. den Ouden (IGZ)
Drs. H. Smid (ZonMW)
Prof. dr. G.H. Visser (UMCU)
Drs. E. van Vliet-Lachotzki (VSOP)

Methodologische adviesraad

Prof. dr. P.M.M. Bossuyt (AMC)
Dr. S. Le Cessie (LUMC)
Dr. H. Groen (UMCG)
Dr. L. Smits (AZM)
Prof. dr. E. Steyerberg (Erasmus MC)

Lijst clusters en contactpersonen Onderzoeksc consortium Verloskunde, Voortplantingsgeneeskunde en Gynaecologie

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Amsterdam				
clustercoördinator	Dhr. B.W.J. Mol		Dhr. J.P. Roovers	Mw. J. Huirne
plaatsvervangend clustercoörd.	Dhr. J. van der Post	Mw. M. Mochtar	Mw. S. Tiersma	Dhr. W. Ankum
research nurse/midwife	Mw. J.J. Bakker/mw. B. vd Goes/mw. V. Verfaillie	Mw. T. de Vries	Mw. S. Bijlsma/mw. M. Jansen	
AMC	Dhr. B.W.J. Mol	Mw. M. Mochtar	Dhr. B.W. Mol	Mw. A. Timmermans
OLVG	Mw. E. van den Akker	Dhr. H. Verhoeve	A.G. Groenendijk	Dhr. P. van Kesteren
Spaarne Ziekenhuis	Mw. I.M. de Graaf		Dhr. R. Hakvoort	
Sj Lucas Andreas	Mw. M. Heres	Dhr. A. Therkow	Dhr. J. Dawson	MW. C. Radder
MC Alkmaar	Dhr. P. Hummel	Mw. Y. van Kasteren	Dhr. A.H. Adriaanse	
Westfries Gasthuis Hoorn	Mw. J. Klinkert			
Kennemer Gasthuis	Mw. P.Pernet		Dhr. R. Schellart	
Flevo Ziekenhuis Almere	Mw. G.Kleiverda	Mw. G. Kleiverda		
Zaans Medisch Centrum	Dhr. J.P.R. Doombos		J. Brouns	
BovenIJ	Dhr. B. Dijkman	Dhr. B. Dijkman	Dhr. B. Dijkman	
VUmc	Mw. M. Bekker	Dhr. P. Hompes	Mw. S. Tiersma	
Tergooi ziekenhuizen	Dhr. H. Visser	Dhr. H. Visser		
Gemini Den Helder	Dhr. J. Friederich		T. Tavernier	
Amstelland Amstelveen	Dhr. A. Mozes			
Waterland Purmerend		F.W. Bouwmeester		
Slotervaart Amsterdam			Mw. A. Duyn	

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Utrecht				
clustercoördinator	Dhr. M. Oudijk	Dhr. F. Broekmans	Dhr. H. van der Vaart	Dhr. P. Graziosi
plaatsvervangend clustercoörd.	Mw. A. Kwee		Dhr. S. Schraffordt	
research nurse/midwife	Mw. M. de Reus/dhr. D. Borman	Mw. M. Kosterman	Dhr. J. Labrie (arts-onderzoeker)	
UMC Utrecht	Dhr. M. Oudijk	Dhr. F. Broekmans	A. Vollebregt	
Gelre Apeldoorn	Mw. A.J.M. Huisjes		Dhr. W. Spaans	
Sj Antonius Nieuwegein	Dhr. E. v. Beek	Mw. T. Cox	Dhr. P. Graziosi	Dhr. S. Veersema
Diakonessenhuis Utrecht	Dhr. N. Schuitemaker		Dhr. P. Scholten	
Meander MC	Mw. I. Evers	E.A. Brinkhuis	Dhr. S. Schraffordt	
Zuwe Hofpoort Woerden			E. Blokhuis	

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Leiden				
clustercoördinator	Mw. K. Bloemenkamp	Dhr. F.M. Helmerhorst	Dhr. F. Milani	Dhr. F.W. Jansen
plaatsvervangend clustercoörd.	Dhr. S. Scherjon		Dhr. J.W. de Leeuw	
research nurse	Mw. C. Kolster/ M. Verhart	Mw. N.F. Klijn		
Leids UMC	Mw. K. Bloemenkamp	Dhr. F. Helmerhorst		
Groene Hart Gouda	Mw. C.A. van Meir		Mw. I. v.d. Wijk	
Bronovo	Dhr. W. v. Wijngaarden			
MC Haaglanden			F. Twaalfhoven	
HAGA Den Haag	Mw. M. van Huizen			
Diaconessenhuis Leiden	Dhr. G.A. van Unnik			
Rijnland Ziekenhuis	Mw. M.J. de Vries			

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Brabant				
clustercoördinator	Mw. M. Porath	Mw. C. Koks	Mw. M. Bongers	Mw. P. Geomini
plaatsvervangend clustercoörd.	Dhr. A. Drogtróp			
research nurse/midwife	Mw. C. Verhoeven / C. v.d. Griendt	Mw. I. van Oosterhout, mw. J. Kitzén		
Maxima MC	Mw. M. Porath	Dhr. B.W. Mol	Mw. M. Bongers	Mw. M. Bongers
Jeroen Bosch Ziekenhuizen	Dhr. R.J.P. Rijnders	Dhr. J.P. de Bruin	Dhr. J.P. de Bruin	
Catharina Ziekenhuis	Dhr. T. Hasaart	P.A. van Dop	Dhr. T. Hasaart	
Twee Steden Ziekenhuis	Dhr. A. Drogtróp	H. van Dessel	Mw. M. Stegeman	
Sf Elisabeth Tilburg	Mw. C.M. van Oirschot	Mw. P. Maas	Dhr. H. Vervest	
Elkerliek Ziekenhuis	Dhr. F. Delemarre		A. van Vijfeijken	
Sf Anna Geldrop	Dhr. J.F.M. Molkenboer			
Sf Franciscus Roosendaal	Mw. E. Timmerman		R. Pal	

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Limburg				
clustercoördinator	Mw. L. Scheepers	Dhr. J. Maas	Mw. M. Weemhoff	Mw. Catshoek
plaatsvervangend clustercoörd.	Dhr. F. Roumen		Dhr. G. Link	
research nurse	Mw. M. Braken-Florax, Mw. C. Wolfs			
Maastricht UMC	Mw. L. Scheepers		Mw. M. Weemhoff	
Atrium MC Heerlen	Dhr. F. Roumen	Dhr. P. Bouckaert	P.H.N.M. Kampschoer	
Laurentius Roermond	Mw. C. Wingen	R. Mulder	Dhr. M. Bergmans	
Vie Curi Venlo	Mw. E.J. Wijnen		I. van Gestel	
Orbis Sittard	Dhr. R. Aardenburg	Dhr. E. Gondrie	Dhr. G. Bremer	
Sf Jans Gasthuis Weert	Dhr. I.M.A. van Dooren		Dhr. I.M.A. van Dooren	

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Groningen				
clustercoördinator	Mw. M. Franssen	Mw. A. Hoek	Dhr. M. van der Ploeg	Mw. M. van den Berg
plaatsvervangend clustercoörd.	Dhr. P. van den Berg	Mw. J. Land	Mw. A.J. Schram	
research nurse	Mw. L. Ulkeman /mw. J. Keurentjes/mw. L.E. Hamming			
UMC Groningen	Mw. M. van Pampus	Mw. A. Hoek	Mw. A. Schram	
Isala Klinieken	Dhr. J. van Eyck	Dhr. B. Cohlen	Dhr. J. den Boon	
Martini Ziekenhuis Groningen	Dhr. A. v. Loon	J. Gerards	Dhr. M. van der Ploeg	
MC Leeuwarden	Mw. D. Perquin	Mw. D. Perquin	Dhr. J. Stekelenburg	Dhr. T. Spinder
Scheper Ziekenhuis Emmen	Dhr. J. Burggraaf	Dhr. J. Burggraaf		
Diaconessenhuis Meppel	Dhr. G.M. Vermeulen			
Nij Smellinghe Drachten	Dhr. J. Wilpshaar		Mw. J. de Vries	
Wilhelmina Ziekenhuis Assen	Dhr. Huijbrechts	A.V. Sluijmer		
Bethesda Zkh Hoogeveen	Mw. M. Hanssen			
Antonius Ziekenhuis Sneek	Dhr. J.E. van de Riet	Mw. M. Wortelboer		

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Zwolle				
clustercoördinator	Dhr. B. Nij Bijvank			
Research nurse	Mw. D. Lutjes			
Isala Klinieken Zwolle	Dhr. B. Nij Bijvank			Dhr. H. van Eijndhoven
Diaconessenhuis Meppel	Dhr. G.M. Vermeulen			

	Verloskunde	Fertiliteit	Urogynaecologie	Benigne gynaecologie
Cluster Rotterdam				
<i>clustercoördinator</i>	<i>Dhr. J.J. Duvekot</i>	<i>Dhr. J. Laven</i>	<i>Dhr. F. Milani</i>	
<i>plaatsvervangend clustercoörd.</i>	<i>Dhr. D. Papatsonis</i>		<i>Dhr. J.W. de Leeuw</i>	
<i>research nurse</i>	<i>J. van Rhee, T. Winter</i>		<i>Mw. N. LeNoble</i>	
Erasmus MC	Dhr. J.J. Duvekot	Dhr. J. Laven		
Ikazia Ziekenhuis	Dhr. J.W. de Leeuw		Dhr. J.W. de Leeuw	
St Franciscus Gasthuis	Mw. N. van Gemund	Alberda	Dhr. B. Broekman	Dhr. M. van Hoof
Reinier de Graaf Delft	Dhr. H. Bremer	H. Kragt	Dhr. F. Milani	
Amphia Breda	Dhr. D.N.M. Papatsonis	Dhr. D. Papatsonis	Mw. I. Smalbraak	
A Schweitzer Dordrecht	Mw. B.M.C. Akerboom	Dhr. L. Lambers	K. Hogewoning	
Lievensberg Bergen op Zoom	Mw. N.J. Noordam			
Van Weel-Bethesda Dirksland	Dhr. J. Vreuls		R. Cikot	
Lange Land Zoetermeer	Mw. M. de Jong			
Zeeuws Vlaanderen Temeuzen	Dhr. C. Reyneke			

Cluster Nijmegen				
<i>clustercoördinator</i>	<i>Dhr. M. Spaanderman</i>	<i>W. Willemse</i>	<i>Dhr. M.E. Vierhout</i>	<i>Dhr. P. Dijkhuizen</i>
<i>plaatsvervangend clustercoörd.</i>	<i>Mw. M. Woiski</i>		<i>Mw. K. Kluivers</i>	
<i>research nurse</i>	<i>Dhr. G. Zijderveld</i>			
UMC St Radboud Nijmegen	Dhr. M. Spaanderman	Dhr. J. Kremer	Dhr. M. Vierhout	Mw. K. Kluivers
Ziekenhuis Rijnstate Arnhem	Mw. K.de Boer	Dhr. L. Bancsi	Aalders	Dhr. P. Dijkhuizen
St Canisius-Wilhelmina	Dhr. J.M.J. Sporken	C.F. van Heteren	J. Stoutjesdijk	
Gelderse Vallei Ede	Dhr. M.J.N. Weinans			
Maasziekenhuis Pantein Boxmeer	Dhr. S. de Wit			
Ziekenhuis Zevenaar	R. Mouw		R. Mouw	
Ziekenhuizen Bernhoven	Mw. A. Versantvoort		Mw. A. Versantvoort	

Cluster Oost				
<i>clustercoördinator</i>	<i>Dhr. M. Sikkema</i>	<i>Dhr. J. Oosterhuis</i>		<i>Dhr. J. Oosterhuis</i>
<i>plaatsvervangend clustercoörd.</i>	<i>Dhr. J. Oosterhuis</i>	<i>Mw. J. Neve</i>		
<i>research nurse</i>	<i>Mw. I. Volker/dhr. E. Lubbers</i>			
Twenteborg Almelo	Dhr. M. Sikkema		Mw. K.S. Dekker	
Med Spectrum Twente Enschede	Dhr. H.P. Quartero	Dhr. J. Oosterhuis	Mw. E. Everhardt	Dhr. J. Oosterhuis
Deventer Ziekenhuis	Dhr. R. Stigter	J.M. Schierbeek	A. Weis	Mw. L.F. van der Voet
Röpke Zweers Hardenberg	Mw. M. Kaplan	Mw. M. Kaplan		

Promovendi

Sylvia Vijgen	Economische analyse	AMC
Arienne Lim	AMPHIA	AMC
Femke Wilms	APOSTEL 1	AMC
Jolande Vis	Diagnostic Information, APOSTEL I	AMC
Margreet Teune	Lange termijn follow-up	AMC
Jeanine van de Ven	Triple P	AMC
Alexandra Bendsdorp	INeS	AMC
Claudia Kowalik	TRUST	AMC
Sophie Liem	ProTWIN	AMC
Marielle Lakeman	Ligasure	AMC
Floortje Vlemmix	Implementatie ECV	AMC
Ageeth Rosman	Implementatie ECV	AMC
Josje Langenveld	HYPITAT II	AMC
Femke Mol	ESEP	AMC
Katrien Oude Rengerink	Optimaliseren inclusies in RCT's	AMC
Brenda Kazemier	ASB	AMC
Femke Mulder	CAMPUR/COMPARE	AMC
Marjet Rutten	LapOvCa	AMC
Merel Breijer	POMPOEN	AMC
Eleni Mantikou	MEDIUM	AMC
Sanne Braam	IVM	AMC
Karin van der Tuuk	HYPITAT	UMCG
Kim Broekhuisen	HYPITAT II	UMCG
Meike Mutsaerts	Lifestyle	UMCG
Jeroen Beckers	Stan follow-up	UMCU
Joepe Kaandorp	ALLO	UMCU
Julien Labrie	PORTRET	UMCU
Karst Heida	APOSTEL III	UMCU
Daphne van Munster	GLucoMOMS	UMCU
Ewoud Schuit	Predictiemodellen	UMCU
Yvonne Koot	PROMISE	UMCU
Vacature	OPTIMIST	UMCU
Vacature	InSIGHT	UMCU
David van der Ham	PPROMEXIL	MUMC
Jantien vd Heyden	PPROMEXIL	MUMC
Denise Delahaye	PreCare	MUMC
Sander van Kuijk	PreCare	MUMC
Ellen Schoorel	SIMPLE	MUMC
Sonja Melman	SIMPLE	MUMC
Kim Notten	TRUDIL	MUMC
Carolien Roos	APOSTEL II	UMC St Radboud
Laura Seinen	APOSTEL II follow-up	UMC St Radboud
Mallory Woiski	Fluxim	UMC St Radboud
Sanne van Leijssen	VUSIS	UMC St Radboud
Marta Jozwiak	PROBAAT	LUMC
Mieke ten Eikelder	PROBAAT II	LUMC

Claartje Huisman	PROBAAT-S	LUMC
Kim Boers	DIGITAT	LUMC
Linda van Wijk	DIGITAT follow-up	LUMC
Liv Freeman	RAVEL	LUMC
Rimke Vos	HTA RAVEL	LUMC
Wietske Hermes	HyRas	VUmc
Susanne Luitjes	BIG CHANGE	VUmc
Melanie van Os	Triple P	VUmc
Marleen Nahuis	M-OVIN'	VUmc
Babette Prick	WOMB	Erasmus MC
Eline van der Wilk	Totem	Erasmus MC
Eva Groenewoud	ANTARCTICA	Isala
Joost van de Ven	TOSTI	Máxima MC Veldhoven
Marjo van Melick	ProTWIN werkbelasting	
Arjanne Kroese	WoMan	

Gepromoveerd

Michelle Westerhuis, STan study, UMC Utrecht 2010

Denise Bijlenga, Kwaliteit van Leven en preferentieonderzoek HYPITAT en DIGITAT, AMC 2010

Corine Koopmans, HYPITAT, UMC Groningen, 2011

Inclusie Verloskunde en Voortplantingsgeneeskunde 2010

Inclusie per studie	Jan	Feb	Mrt	Apr	Mei	Juni	Juli	Aug	Sept	Okt	Nov	Dec
PPROMEXIL	20	16	13	14	15	11	16	12	19	14	24	6
WOMB	15	11	11	9	4	9	9	13	16	4	7	9
PreCare	8	8	3	3	4	6	1	3	8	6	16	7
HYPITAT II	24	14	17	9	11	15	17	17	17	9	20	22
ProTWIN	7	18	12	17	30	35	28	31	32	34	37	26
ALLO	4	3	4	10	5	4	10	11	9	14	8	8
Triple P	0/72 [#]	1/103 [#]	1/146 [#]	1/111 [#]	0/247 [#]	1/252 [#]	2/224 [#]	0/320 [#]	3/510 [#]	4/530 [#]	0/598 [#]	3/376 [#]
APOSTEL I	0/4 [#]	1/5 [#]	0/10 [#]	3/10 [#]	2/10 [#]	5/28 [#]	3/24 [#]	1/12 [#]	6/30 [#]	6/30 [#]	2/42 [#]	4/32 [#]
CHIPS	1	2	4	2	2	0	0	0	0	2	1	2
ESEP (NL)	7	1	6	0	1	1	5	2	6	5	2	2
Lifestyle	10	23	28	19	11	19	17	8	24	25	24	16
INeS	20	23	23	22	14	14	23	19	19	23	22	13
Antarctica	12	8	16	21	17	30	17	10	16	10	19	17
IVM	2	5	10	4	5	3	2	2	4	5	3	3
M-OVIN'	6	6	4	4	5	3	9	6	14	3	6	4
PROMISE	-	-	-	-	-	-	-	2	9	1	8	3
APOSTEL II	10	2	-	-	-	-	-	-	-	-	-	-
PROBAAT	130	122	133	119	58	-	-	-	-	-	-	-
TRUFFLE,NL	1	3	2	3	2	0	6	9	2	-	-	-
TOTAAL	147*	145*	154*	143*	136*	161*	167*	153*	210*	164*	199*	145*

*excl. PROBAAT en cohort APOSTEL I en Triple P (wel randomisaties)

[#]inclusie in cohortdeel van de studie

Inclusie per cluster	2010											
	Jan	Feb	Mrt	Apr	Mei	Juni	Juli	Aug	Sept	Okt	Nov	Dec
Cluster Amsterdam	38	44	35	42	32	44	35	29	57	32	49	36
Cluster Brabant	12	16	34	30	19	20	29	24	36	19	31	18
Groningen	17	27	25	11	15	18	20	17	25	12	18	20
Zwolle	2	1	3	10	20	19	14	9	18	14	14	16
Cluster Leiden	13	5	4	2	7	9	9	8	11	5	6	5
Cluster Limburg	13	6	13	8	8	10	12	5	12	16	16	6
Cluster Nijmegen	3	6	4	2	3	8	6	8	8	11	9	4
Cluster Rotterdam	16	13	13	14	11	13	18	22	10	17	26	11
Cluster Twente	3	6	10	7	6	9	8	5	11	13	7	12
Cluster Utrecht	27	17	13	17	15	11	16	26	26	25	23	17
Totaal	147	145	154	143	136	161	167	153	210	164	199	145