Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation

The INeS Study Group

EDITORIAL by Romundstad and colleagues

Correspondence to: M van Wely, Centre for Reproductive Medicine, Academic Medical Centre, University of Amsterdam, 1100 DD Amsterdam, Netherlands
m.vanwely@amc.nl

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STUDY QUESTION

Can multiple pregnancies be prevented while maintaining live birth rates in couples with unexplained or mild male subfertility by treating with in vitro fertilisation with single embryo transfer or in vitro fertilisation in a modified natural cycle instead of standard treatment with intrauterine insemination with controlled ovarian hyperstimulation?

SUMMARY ANSWER

In vitro fertilisation with single embryo transfer and in vitro fertilisation in a modified natural cycle were non-inferior to intrauterine insemination with controlled ovarian hyperstimulation in terms of the birth of a healthy child and showed comparable, low multiple pregnancy rates.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Intrauterine insemination with controlled ovarian hyperstimulation is the first line treatment in subfertile couples with unexplained or mild male subfertility and unfavourable chances of natural conception, but concern exists about increased rates of multiple pregnancy.
There seems to be no reason to abandon intrauterine insemination with controlled ovarian hyperstimulation as a first line treatment of couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception.

Design

This was a multicentre, open label, three arm, parallel group, randomised controlled non-inferiority trial. Couples were randomly allocated to receive either three consecutive cycles of in vitro fertilisation with single embryo transfer plus subsequent cryocycles, six consecutive cycles of in vitro fertilisation in a modified natural cycle, or six consecutive cycles of intrauterine insemination with controlled ovarian hyperstimulation. We included all interventions that couples received within 12 months after randomisation.

Participants and setting

Eligible couples were those seeking fertility treatment after at least 12 months of unprotected intercourse, with the female partner aged between 18 and 38 years, an unfavourable prognosis for natural conception, and a diagnosis of unexplained or mild male subfertility. They were treated in fertility clinics in the Netherlands.

Primary outcome(s)

The primary outcome was the birth of a healthy child resulting from a singleton pregnancy conceived within 12 months after randomisation.

Main results and the role of chance

Birth of a healthy child occurred in 104 (52%) couples after in vitro fertilisation with single embryo transfer, 83 (43%) after in vitro fertilisation in a modified natural cycle, and 97 (47%) after intrauterine insemination with controlled ovarian hyperstimulation. The two 95% confidence intervals for comparison of in vitro fertilisation with single embryo transfer or in a modified natural cycle versus intrauterine insemination with ovarian hyperstimulation did not extend below the predefined threshold of 0.69 for inferiority. Multiple pregnancy rates per ongoing pregnancy were comparable and low.

Harms

Two women in the in vitro fertilisation with single embryo transfer group and one woman in the intrauterine insemination with controlled ovarian hyperstimulation group developed ovarian hyperstimulation syndrome.

Bias, confounding, and other reasons for caution

Baseline characteristics were well balanced between the three arms, giving no reason to conclude that confounding affected the results.

Generalisability to other populations

This study provides new evidence on the effectiveness and safety of in vitro fertilisation with single embryo transfer, in vitro fertilisation in a modified natural cycle, and intrauterine insemination with controlled ovarian hyperstimulation in couples with unexplained or mild male subfertility. Whether our findings can also be used to counsel couples with a female age above 38 years is unclear.

Study funding/potential competing interests

The study was supported by grants from ZonMW, the Dutch Organization for Health Research and Development, and Zorgverzekeraars Nederland, the Dutch association of healthcare insurers.

Trial registration number

Current Controlled Trials ISRCTN52843371; Nederlands Trial Register NTR939.

Summary of main outcomes

Outcome	IVF-SET (n=201)	IVF-MNC (n=194)	IUI-COH (n=207)	Relative risk (95% CI)	
				IVF-SET *v* IUI-COH	IVF-MNC *v* IUI-COH
Healthy child	104 (52)	83 (43)	97 (47)	1.10 (0.91 to 1.34)	0.91 (0.73 to 1.14)
Multiple pregnancy*	7 (6)	5 (5)	8 (7)	0.86 (0.32 to 2.30)	0.73 (0.25 to 2.16)

IUI-COH=intrauterine insemination with controlled ovarian hyperstimulation; IVF-MNC=in vitro fertilisation in modified natural cycle; IVF-SET=in vitro fertilisation with single embryo transfer.
*Percentage is ratio of total ongoing pregnancies. Three monochorial twins: two in IVF-MNC group and one in IUI-COH group.

Long term mental health outcomes of Finnish children evacuated to Swedish families during the second world war and their non-evacuated siblings: cohort study

Torsten Santavirta,[1] Nina Santavirta,[2] Theresa S Betancourt,[3] Stephen E Gilman[4]

EDITORIAL by Silove

[1]Swedish Institute for Social Research, Stockholm University, SE-10691, Stockholm, Sweden
[2]Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland
[3]Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA
[4]Department of Social & Behavioral Sciences and Department of Epidemiology, Harvard School of Public Health, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
Correspondence to: T Santavirta
torsten.santavirta@sofi.su.se

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STUDY QUESTION

Did the Finnish policy of evacuating children to foster families in Sweden during the second world war confer long term harms on mental health, as measured by the risk of hospital admission for a psychiatric disorder in adulthood?

SUMMARY ANSWER

The risk of being admitted for any mental disorder was decreased among men but among women was increased for mood disorders.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous studies evaluating the long term effects of the Finnish evacuation policy were subject to confounding biases: evacuation was highly dependent on family characteristics that were themselves likely to increase the risk for mental health problems in children. The Finnish evacuation policy was not significantly predictive of admission to hospital for a psychiatric disorder during adulthood.

Participants and setting

Children born in Finland during 1933-44 who were later included in a 10% sample of the 1950 Finnish census ascertained in 1997 (22 021 women; 23 442 men). We identified evacuees in the sample from war time government records.

Design, size, and duration

This was an observational cohort study using data of children born during 1933-44 and linked to the 1950 and 1971 Finnish census and to the Finnish hospital discharge register for 1971-2011. We used Cox proportional hazards models to estimate the association between evacuation to temporary foster care in Sweden during the second world war and hospital admission for psychiatric disorders between ages 38 and 78 years. We estimated the association between evacuation and hospital admission for a psychiatric disorder using conventional cohort methods and using fixed effects methods that control for all unobserved social and genetic characteristics that are shared among siblings.

Main results and the role of chance

Among men and women combined, the risk of admission to hospital for a psychiatric disorder did not differ between Finnish adults evacuated to Swedish foster families and their non-evacuated siblings (hazard ratio 0.89, 95% confidence interval 0.64 to 1.26). Evidence suggested a lower risk of admission for any mental disorder (0.67, 0.44 to 1.03) among evacuated men, whereas for women there was no association between evacuation and the overall risk of admission for a psychiatric disorder (1.21, 0.80 to 1.83).

Bias, confounding, and other reasons for caution

The conventional cohort analyses are subject to between family selection effects that are likely to bias the results upwards (children from worse backgrounds being likely to attend the program and to have psychiatric disorders during adulthood). This source of bias is virtually eliminated by use of a stable within sibling design that adjusts for confounders shared by the siblings. None the less, residual confounding could arise if families disproportionately selected their most resilient or most vulnerable child for evacuation. The available evidence does not suggest that this was the case.

Generalizability to other populations

The displacement of children because of armed conflict is a major humanitarian crisis. Our study highlights the conflicting interests of shielding children from the direct consequences of armed conflict versus exposing them to interventions that may have long term adverse effects on their mental health.

Study funding/potential competing interests

All researchers are independent of the study funders, Academy of Finland, National Institutes of Health (grant MH087544), Signe and Ane Gyllenberg Foundation, Tore Browaldh Foundation, and Siamon Foundation.

Within sibling analyses for risk of hospital admission for a psychiatric disorder at age 38-78 (1971-2011) according to evacuee status as child during second world war

	Hazard ratio (95% CI)		
Psychiatric disorder	All (n=45 463)	Women (n=22 021)	Men (n=23 442)
Any	0.89 (0.64 to 1.26)	1.21 (0.80 to 1.83)	0.67 (0.44 to 1.03)
Mood	1.39 (0.82 to 2.37)	2.19 (1.10 to 4.33)	0.90 (0.44 to 1.83)

Quantifying and monitoring overdiagnosis in cancer screening: a systematic review of methods

Jamie L Carter,[1] Russell J Coletti,[2] Russell P Harris[3]

[1]Department of Medicine, University of California, San Francisco, San Francisco, CA 94110, USA
[2]Division of General Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
[3]Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
Correspondence to: R P Harris
russell_harris@med.unc.edu

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TOO MUCH MEDICINE

STUDY QUESTION

What methods have been used for measuring overdiagnosis from cancer screening, and what are the strengths and weaknesses of each method?

SUMMARY ANSWER

Of the four major research methods that have been used to measure overdiagnosis from cancer screening (modeling studies, pathological and imaging studies, ecological and cohort studies, and follow-up of randomized controlled trials), well conducted ecological and cohort studies in multiple settings are the most appropriate approach for quantifying and monitoring overdiagnosis in cancer screening programs.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Studies of cancer overdiagnosis using various methods found a wide range of results, but it was unclear how to evaluate the methods in order to interpret the conflicting results. This systematic review evaluated risk of bias and strength of evidence to assess each of the methods for providing valid and reliable estimates of the frequency of overdiagnosis and the suitability for monitoring overdiagnosis over time.

Selection criteria for studies

We searched PubMed and Embase for studies of any design that quantified overdiagnosis of cancer resulting from screening in an asymptomatic population.

Primary outcome(s)

We evaluated studies and the body of evidence for risk of bias, directness, analysis, time frame, external validity, precision, and consistency.

Main results and role of chance

From the 52 studies that met the inclusion criteria, we identified four major research methods that have been used to measure overdiagnosis from cancer screening: modeling studies (21 studies), pathological and imaging studies (8), ecological and cohort studies (20), and follow-up of a randomized controlled trial (3). Using the frameworks for evaluating risk of bias and strength of evidence, we identified strengths and weaknesses of each of these methods for providing valid and reliable estimates of the frequency of overdiagnosis and the suitability for monitoring overdiagnosis over time (table).

Follow-up of a randomized trial is ideal for internal validity but requires extended time, may lack external validity, and is not useful for monitoring. Modeling studies and pathological and imaging studies are simpler to perform but introduce uncertainty by lack of directness and requiring assumptions about cancer progression. Ecological and cohort studies can be limited by confounding and require careful analysis, but when performed well they can provide a more valid and reliable estimate of overdiagnosis. They are also well designed to monitor and compare screening programs over time.

Bias, confounding, and other reasons for caution

We had to modify criteria for strength of evidence to fit the different research designs; readers should examine these criteria when interpreting our findings.

Study funding/potential competing interests

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Strengths and weaknesses of the main research methods used to quantify overdiagnosis from cancer screening

Research method	Strengths	Weaknesses
Follow-up of randomized controlled trials	Best able to minimize biases Directly answers question of interest	Substantial time and resource requirements Limited external validity Not useful for monitoring over time
Modeling	Can project through areas of uncertainty Not limited by time constraints Can evaluate multiple screening situations Can be used for monitoring over time	Validity of results depends on assumptions (poor directness) Needs constant updating of model constraints to reflect changing nature of cancer diagnosis and treatment Small changes in assumptions and model can lead to large changes in estimates Difficult to critically appraise (a "black box") Need long follow-up to determine overdiagnosis, yet uncertainty increases with time in models May give false sense of precision, insufficient attention to uncertainty
Pathological and imaging studies	Can be used for monitoring over time One of the simplest approaches	Validity of results depends on assumptions (poor directness) Not able to account for competing mortality Need to be sure all diagnosed cases are ascertained, and that data are collected in same way
Ecological and cohort studies	Directly answers question of interest Provides "real world" view of overdiagnosis Able to compare results from different settings Can be used for monitoring over time	Potential for confounding factors related to diagnosis, treatment, and health status between populations Moderate time requirements Needs investment in population registries, full and accurate ascertainment of all cases, and full and accurate collection of potential confounders

Long working hours and alcohol use: systematic review and meta-analysis of published studies and unpublished individual participant data

The IPD-Work Consortium

EDITORIAL by Okechukwu

Correspondence to: M Virtanen
marianna.virtanen@ttl.fi

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STUDY QUESTION

Are individuals who work long hours more likely to increase their alcohol use to levels that pose a health risk compared with those who work standard hours?

SUMMARY ANSWER

Individuals whose working hours exceed standard recommendations are more likely to increase their alcohol use to levels that pose a health risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The European Union Working Time Directive threshold for long working hours is 48 hours a week. Though individuals who work long hours are known to be at an increased risk of health problems, the association between long working hours and risky alcohol use has not been systematically evaluated. This systematic review and meta-analysis of published studies and studies with unpublished individual participant data synthesised evidence on the association between long working hours and risky alcohol use. Individuals whose working hours exceeded standard recommendation of 48 hours a week used more alcohol than those who worked 35-40 hours a week. In the prospective analysis, individuals working more than 48 hours a week were also more likely to increase their alcohol use to risky levels.

Selection criteria for studies

We included 36 empirical and peer reviewed published studies reporting cross sectional or prospective association between working hours and alcohol use. Additional unpublished individual participant data were obtained from 27 studies.

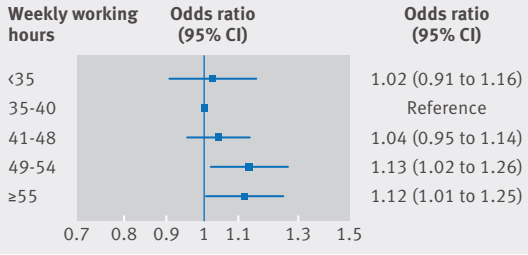
Primary outcome

Alcohol use and alcohol use above the recommended limit (risky alcohol use).

Main results and role of chance

The pooled maximum adjusted odds ratio for the association between long working hours and alcohol use was 1.11 (95% confidence interval 1.05 to 1.18) in the cross sectional analysis. Odds ratios of new onset risky alcohol use for working 49-54 hours and ≥55 hours a week were 1.13 (1.02 to 1.26) and 1.12 (1.01 to 1.25), respectively, compared with working standard 35-40 hours. No heterogeneity was observed between men and women or by age group, socioeconomic status, geographical region, or characteristics of the study cohort. The differences were relatively small because the adjusted incidence in new onset risky alcohol use was 0.8 and 0.7 percentage points higher among individuals who worked 49-54 and ≥55 hours, respectively, compared with those who worked standard hours.

Pooled association between weekly working hours and new onset risky alcohol use, adjusted for sex, age, socioeconomic status, and ethnicity at baseline



Bias, confounding, and other reasons for caution

The observed association is not necessarily causal. In observational data, such as these, residual confounding and reverse causation remain an alternative explanation for the association.

Study funding/potential competing interests

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