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Chapter 5

Natural conception rates in couples with unexplained or mild male subfertility scheduled for fertility treatment: a secondary analysis of a randomized controlled trial

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Abstract

Study question: What is the natural conception rate over the course of 12 months in couples with unexplained or mild male subfertility who are scheduled for fertility treatment and have a predicted unfavourable prognosis for natural conception?

Summary answer: The natural conception rate over the course of 12 months in couples who were allocated to treatment was estimated to be 24.5% (95%CI: 20% to 29%).

What is known already: After starting treatment, couples often perceive unsuccessful cycles as evidence of definitive failure even though they are still able to conceive naturally in between and after treatment. The magnitude of the natural conception rate for couples who chose to commence treatment is unknown, as is whether the calculated prognosis before commencing treatment is still applicable.

Study design, size, duration: We performed a secondary analysis of a randomised controlled trial including couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception. Couples were allocated to either three cycles IVF with single embryo transfer (SET), six cycles of IVF in a modified natural cycle (MNC) or six cycles of intrauterine insemination with controlled ovarian hyperstimulation (IUI-COH). The detailed data collection in this trial allowed us to study the conception rates in periods that couples were not receiving treatment.

Participants/materials, settings, methods: We split the dataset into periods during which couples were treated and periods during which they were not treated. Couples could conceive naturally in the periods before, in between and after treatment cycles. The outcome was ongoing pregnancy, thus natural conception rate refers to natural conception leading to ongoing pregnancy. We performed a Cox proportional hazards analysis with female age, duration of subfertility and a time-varying covariate with four categories: IVF-SET, IVF-MNC, IUI-COH and no treatment. We used this Cox model to estimate the natural conception rate over 12 months of no treatment.

Main results and the role of chance: Out of 602 included couples, there were 342 ongoing pregnancies, of which 77 (23%) resulted from natural conception. The estimated natural conception rate over 12 months was 24.5% (95%CI: 20% to 29%) on cohort level. Estimated rates for female age varying between 18 and 38 years and duration of subfertility between 1 and 3 years ranged from 22% to 35%.

Limitations, reasons for caution: We considered couples at risk for natural conception when not receiving treatment, whereas they might not have had periovulatory sexual intercourse. As couples were scheduled for treatment, it is possible that these couples were less inclined to try to conceive naturally, potentially leading to an underestimation of their natural conception rate if they kept trying to conceive.

Wider implications of the findings: Couples with unexplained subfertility who are about to start fertility treatment, still have about a one in four chance of ongoing pregnancy due to natural conception over 12 months. This information can add to the counselling of couples who commenced fertility treatment after failed cycles and to emphasize not to cease their natural attempts.

Study funding/competing interest(s): The INeS trial was supported by a grant from ZonMW, the Dutch Organization for Health Research and Development (120620027), and a grant from Zorgverzekeraars Nederland, the Dutch association of health care insurers (09-003). The funders had no role in study design, collection, analysis and interpretation of the data. BWM is supported by a NHMRC Practitioner Fellowship (GNT1082548). BWM reports consultancy for ObsEva, Merck and Guerbet. No other potential conflicts of interest reported.

Trial registration number: The INeS trial was registered at the Dutch trial registry (NTR 939).

Introduction

Nearly half of all couples that are subfertile, defined as 12 months of unsuccessful, unprotected intercourse, have unexplained or mild male subfertility (Brandes *et al.*, 2010). Couples are diagnosed as such when routine fertility investigations show no abnormalities or a mild sperm factor. As these couples may still be able to conceive naturally, medically assisted reproduction is typically only offered to those deemed to have low chances of natural conception (ASRM, 2006; NVOG, 2010; NICE, 2013). The probability that a couple may conceive naturally is thus crucial to clinical decision-making for couples with unexplained subfertility.

After commencing treatment, couples often perceive unsuccessful cycles as evidence of definitive failure, even though they are still able to conceive naturally in between and after treatment. The natural conception rate in couples in a treatment pathway is unknown, because the large observational cohort studies on natural conception did not study subfertile couples after starting treatment. Instead, time-to-pregnancy for treated couples was censored i.e. these couples were removed from the cohort when they started treatment, because the time spent on expectant management before treatment was the main interest (Hunault *et al.*, 2004; van der Steeg *et al.*, 2007; van Eekelen *et al.*, 2017). It is thus not clear whether the resulting prognosis for natural conception is applicable to couples who started treatment but failed to conceive.

The recent INeS trial included couples with unexplained or mild male subfertility and an unfavourable prognosis of natural conception, defined as less than 30% chance to conceive naturally leading to live birth over the year after the fertility workup as calculated using the Hunault model, and randomised couples between two types of IVF and IUI using ovarian stimulation (Hunault *et al.*, 2004; Bendsorp *et al.*, 2015). Although all couples had been allocated to treatment, almost a quarter of all ongoing pregnancies were due to natural conception (77 out of 342). This indicates that natural conception occurs in couples who are in a treatment trajectory, but this is not easily interpretable as a prognosis or a rate because one should express the number of natural conceptions relative to the duration in which couples could conceive naturally i.e. the time off treatment.

The aim of the present study was to investigate the natural conception rate in couples with unexplained or mild male subfertility who are about to start fertility treatment, taking into account the periods of no treatment before, in between and after treatment cycles over the course of 12 months after randomisation.

Materials and Methods

We used data from the INeS trial that included 602 couples with unexplained or mild male subfertility, recruited between January 2009 and February 2012 in the Netherlands (Bensdorp *et al.*, 2015). Couples were eligible for the study when seeking fertility treatment after at least 12 months of unprotected intercourse, if the female partner was between 18 and 38 years, if they had been diagnosed with unexplained or mild male subfertility and if they were categorised as having an unfavourable prognosis for natural conception, defined as a predicted probability using the Hunault model of less than 30% to conceive naturally leading to live birth, over the year after the fertility-workup (Hunault *et al.*, 2004). Unexplained subfertility was defined as at least one patent fallopian tube, an ovulatory menstrual cycle, and a semen analysis within the normal range. Mild male subfertility was defined as a total motile sperm count between 3 and 10 million.

Consenting couples were randomly allocated to either 3 cycles of IVF with single embryo transfer (IVF-SET) and subsequent frozen thawed embryo transfers, 6 cycles of IVF in a modified natural cycle (IVF-MNC) or to 6 cycles of IUI with controlled ovarian hyperstimulation (IUI-COH). The trial has been reported in detail elsewhere (Bensdorp *et al.*, 2015).

We used ongoing pregnancy as the outcome, defined as a registered heartbeat of a fetus at or beyond 12 weeks of gestation. Natural conception rate in the context of this study thus refers to natural conception leading to ongoing pregnancy, expressed over 12 months since couples were followed until 12 months after randomisation. The date of ongoing pregnancy was defined as the first day of the last menstrual period before conceiving, leading to ongoing pregnancy.

Analysis

Couples were considered at risk for natural conception in the periods before, between and after treatment. We split the dataset into periods during which couples were treated and periods during which they were not treated, with follow-up starting at randomisation. We performed a Cox proportional hazards analysis with time to ongoing pregnancy as the outcome using female age, duration of subfertility and a time-varying covariate with four categories: IVF-SET, IVF-MNC, IUI-COH and no treatment as predictors. We checked the proportional hazards assumption of the model and added time-varying effects of predictors over time when necessary. See **Supplementary material I** for more details regarding time periods and modelling. We used the model to estimate the natural conception rate over 12 consecutive months on cohort level and visualized this in a curve. In addition, we estimated natural conception rates for couples with a female age varying between 18 and 38 years and duration of subfertility varying between 1 and 3 years, both at the time of randomisation. All statistical analyses were performed using SPSS version 20.0 (IBM SPSS Statistics for Windows, 2011) and R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

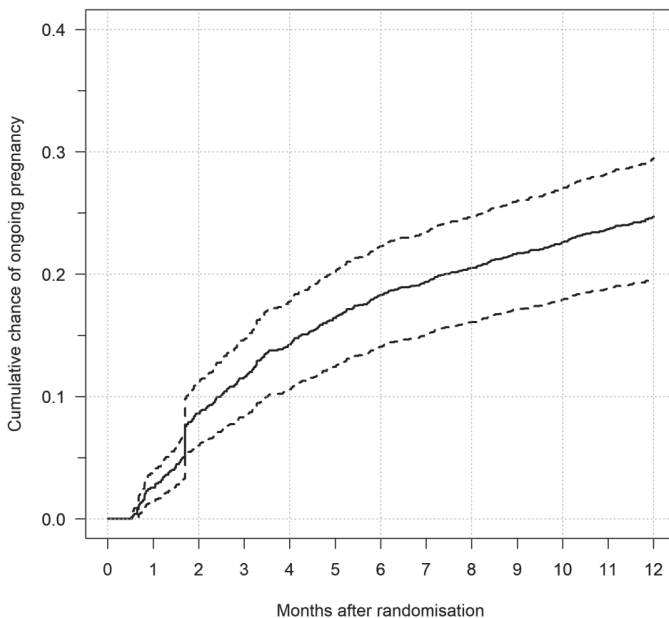
The baseline characteristics of the 602 couples included in the INeS trial are shown in **Table I**.

The mean female age was 33.6 years and the mean duration of subfertility was 2.6 years. Baseline characteristics of couples who conceived naturally were similar to those who achieved an ongoing pregnancy after treatment. The number of couples not being treated, as well as those receiving IVF-SET, IVF-MNC or IUI-COH, which changes over the course of the 12 month follow-up, are depicted in **Supplemental material II**. At randomisation i.e. the start of the follow-up, 98 couples started treatment immediately and 504 couples had not yet started. During follow-up, there were at least 200 couples not undergoing treatment at any given time. Six couples were lost to follow-up before 12 months.

Table I. Baseline characteristics

n=602	Mean or n	5th-95th percentile or %
Female age , in years	33.6	27 – 38
Duration of subfertility, in years	2.6	1.28 – 5.2
Primary subfertility vs. secondary subfertility	458	76%
Progressively motile semen, %	44	14 – 72
Referral by secondary care vs. referral by general practitioner	72	14%

Figure 1. Estimated cumulative natural conception rate leading to ongoing pregnancy after 12 months of sexual intercourse derived from the Cox model. The leap in the model was due to pregnancies in the second month of follow up that could not be traced to a specific date following sonography, which were set at the same follow up.



There were 342 ongoing pregnancies within 12 months after randomisation, 77 (23%) of which after natural conception.

The Cox model containing female age, duration of subfertility and a time-varying covariate for treatment was improved by adding an interaction between treatment and follow-up. Using this model, the estimated cumulative natural conception rate at 12 months is shown in **Figure 1** and was 24.5% (95%CI: 19% to 29%).

Estimated natural conception rates for varying female age and duration of subfertility are shown in **Table II** and ranged from 22% to 35%.

Table II. Estimated natural conception rates leading to ongoing pregnancy for different female age and duration of subfertility

Female age in years	Duration of subfertility in years	Estimated natural conception rate over 12 months (95% CI)
18	1	35% (19-49)
18	2	33% (18-45)
18	3	31% (17-42)
23	1	33% (21-43)
23	2	30% (20-39)
23	3	28% (19-37)
28	1	30% (22-38)
28	2	28% (21-34)
28	3	26% (19-32)
33	1	28% (21-34)
33	2	26% (20-31)
33	3	24% (19-28)
38	1	25% (19-32)
38	2	24% (18-29)
38	3	22% (16-27)

Discussion

In this short commentary, we estimated the natural conception rate leading to ongoing pregnancy to be 24.5% after 12 months in couples with unexplained or mild

male subfertility scheduled for fertility treatment, with estimated rates ranging from 22% to 35% depending on female age and duration of subfertility.

A strength of this study is that we were able to incorporate the time before, between and after treatment thereby utilizing follow-up time of the couples at risk for natural conception that have not been studied in previous cohorts. Since this secondary analysis is based on the data of a randomised controlled trial, there were stringent guidelines for quality control of data collection and management, leading to better quality data and little loss-to-follow-up compared to observational cohorts.

A potential limitation of this analysis is that we considered couples to be at risk for natural conception during the periods they were not treated, but we did not record the actual frequency and timing of sexual intercourse. This could lead to an underestimation of the real natural conception rates since couples could fail to have periovulatory sexual intercourse, which may be likely considering these couples entered treatment trajectories that are generally perceived as stressful. On the other hand, this might be considered a common characteristic of couples who start treatment and therefore our estimates reflect real world natural conception rates for those couples.

The predictive effects of female age and duration of subfertility for ongoing pregnancy were not as apparent as in previous research that focuses on natural conception in the absence of treatment (van Eekelen *et al.*, 2017). This could be because the group was more homogenous, leading to smaller differences between couples.

Our estimate of the natural conception rate of 24.5% on cohort level and ranging estimates of 22% to 35% at varying female age and duration of subfertility coincide with the average Hunault prognosis of couples in the INeS trial of 27% and, in addition, are quite similar to rates found in previously reported prospective cohort studies in couples with unexplained subfertility where treated couples were censored, which ranged from 18% to 37% (Hunault *et al.*, 2004; van Eekelen *et al.*, 2017).

Thus, the selection eligible for treatment in the Netherlands which was included in the INeS trial was similar to the broader population of unexplained subfertile couples from previous research. In addition, the censoring seems to have resulted in accurate natural conception rates also for those couples who start treatment, suggesting that treatment censoring may be considered non-informative in such analyses (van Geloven *et al.*, 2014).

In conclusion, unexplained subfertile couples who start treatment still have a chance of one in four to conceive naturally within one year before, between or after treatment cycles. These findings should be reported to unexplained subfertile couples who are considering or commencing treatment, as it will add to evidence-based counselling and it is important to emphasize not to cease their natural attempts.

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Supplementary material I. Details regarding treatment period definitions and Cox

Couples were considered at risk for natural conception in the periods before, between and after treatment. We split the dataset into periods during which couples were treated and periods during which they were not treated, with follow-up starting at randomisation. The date of ongoing pregnancy was defined as the first day of the last menstrual period before conceiving, leading to ongoing pregnancy.

To create a dataset with a continuous follow-up where couples were either receiving treatment or not, we considered date of starting ovarian stimulation as the start of treatment. We assumed the treatment cycle ended 21 days after this date, as this represents a 'lower limit' i.e. conservative amount of time spent on treatment, which means more time spent on expectant management and a resulting conservative estimate for the natural conception rate. If there were less than two weeks until the next date of treatment, we considered this a treatment period where couples received consecutive cycles as no additional natural cycle could occur within this timeframe. We repeated this process of determining who received which treatment at what time until 12 months after randomisation.

We then performed a Cox proportional hazards analysis with time to ongoing pregnancy as the outcome using female age, duration of subfertility and a time-varying covariate with four categories: IVF-SET, IVF-MNC, IUI-COH and no treatment. To ensure a correct fit of the model, we checked the proportional hazards assumption for treatment effects that remain similar over time by using chi-square tests on scaled Schoenfeld residuals (Grambsch and Therneau, 1994). If this assumption was rejected, the model was improved by also including an interaction between treatment and follow-up, allowing treatment effects to vary over time. For this interaction, we first divided the dataset into short periods of follow-up between unique event times, resulting in a much larger dataset where every row only covers a small portion of follow-up for every individual couple. Using this new dataset, every treatment category was multiplied by follow-up to create an interaction dummy per category per time period. We fitted the model again including the interaction terms. We estimated the natural conception rate for 12 consecutive months of sexual intercourse on cohort level and visualized this in a curve. We

estimated natural conception rates for couples with different female age and duration of subfertility at randomisation.

Supplementary material II. Number of participants per treatment group over follow up

