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The impact of disturbances in natural conception cycles

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Abstract

Purpose Many physicians and other healthcare professionals are often asked questions on interfering factors for conception by couples with a desire for children. Such possible disturbances include, for example, the very common minor diseases, stress and also sexual intercourse during the suspected implantation period. Non-scientifically based statements about disturbances in conception cycles, as found in many layman publications and on the internet, can strongly unsettle couples with a desire for children and force them into corset of rules of conduct. Therefore, a systematic scientific evaluation of the impact of disturbances on conception is urgently needed.

Methods A search for possible disturbances in natural conception cycles together with up to three of the respective pre-cycles in a large cycle database from users of the symptothermal method of natural family planning in Germany was performed. Disturbances were qualified by scientific panel decision and analysed statistically with their effects on the chances of spontaneous conception. Mixed logistical regression models and survival time analyses were used.

Results A total of 237 women with a total of 747 cycles could be included in the analysis. In 61% of all 237 conception cycles, disturbances occurred. The statistical analysis shows that disturbances in natural conception cycles unexpectedly increase the likelihood of pregnancy by an overall factor of 1.32 (95% CI 1.04–1.70). Sexual intercourse in the window of implantation does not decrease the chances of conception. Relaxation states at the time of ovulation and/or during the implantation period have no representable effect and do not increase the chance of pregnancy.

Conclusions Couples trying to conceive should at least be informed that disturbances in conception cycles, such as minor diseases, stress or sexual intercourse during the implantation period do not interfere with conception. Relaxation has no effect in favour of success. This takes away the guilty feeling of couples, fearing that they possibly did something wrong in cycles without the desired pregnancy.

Keywords Spontaneous conception · Implantation · Natural family planning · Probability of pregnancy · Minor diseases · Disturbances of conception

Introduction

For all couples wishing to have children, it is of great importance to know which factors (health, lifestyle, everyday factors like stress) favour or possibly disturb conception. Above all, the question of the impact of possible disorders or disturbances is often addressed to health profesionals who care for couples with desire to have children. Scientific publications on this subject are very rare [1]. But layman publications and the Internet are full of more or less well-founded statements about the role disturbances in the event of a desire for children.

Of course, possible disturbances in a conception cycle include all serious diseases that require medical treatment.

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Their possibly negative impact is well known. But to our knowledge, there is no systematic scientific study on the role of much more common minor diseases[1] and state disorders (e.g., colds, pain, fever, physical stress reactions, sexual intercourse in the implantation phase) in a conception cycle. The same applies to potentially beneficial factors, such as physical and mental relaxation in the conception cycle, which is certainly one of the most frequently mentioned "well-intentioned advices" for couples wishing to have children. In this respect, too, any systematic scientific investigation is lacking for natural conception.

Unfounded statements about possible disturbances in conception cycles can force affected couples into an unnecessary corset of rules of conduct and, above all, significantly increase the sensitivity of stress in those who undergo infertility therapy.

A literature research in the large databases on the question of the impact of possible disturbances in natural cycles of conception led to few studies which investigated the role of stress and sexual intercourse (see below). There are more scientific studies on the role of possible disturbances in fertility therapy cycles in subfertile couples, especially with regard to the immunological processes in the context of implantation, recurrent abortions and multiple unsuccessful IVF cycles. Thus, the findings are mainly findings from pathophysiological constellations and the findings obtained are also very contradictory. Therefore, spontaneous conception cycles must be investigated to rule out the impact of possible disturbances and their effects on conception probabilities.

Materials and methods

Patients

We have consulted the large cycle database of the Section Natural Fertility of the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF e.V.) and the University of Heidelberg. As of December 31, 2016, this database included 43,999 cycles of 1900 users with 504 fully documented clinical pregnancies. The whole data were collected prospectively since 1985 and this long-term study is still ongoing. The data were evaluated regarding the impact of possible disorders in conception cycles until the setpoint of December 31, 2016.

This long-term study was conducted in accordance with the principles of the Helsinki declaration of the World Medical Association. All participants have signed informed consents and agreed in using their anonymized data for scientific purposes.

This database was originally built for the scientific evaluation of natural family planning in Germany regarding acceptance and safety, and currently supports the application of methods for natural contraception scientifically. The basis is the use of the symptothermal method of natural family planning (later called Sensiplan®). The cycles are evaluated according to the so-called "double-check" principle: two parameters each secure both the beginning and the end of the fertile window [2]. There is a high correlation between the cycle parameters used (cervical mucus, temperature rise and calculation rules) with objective ovulation [3, 4]. Ovulation in cycles in which Sensiplan is applied is in 81% about 1–2 days before the temperature rise (mean of 0.92 ± 1.17 days before temperature rise) or 0.11 ± 1.31 days after the day of peak cervical mucus. Using both parameters, 89% of clinical ovulations are within in an interval ± 1 day to objective ovulation confirmed by vaginal ultrasound [3]. For this study, both parameters were used to locate ovulation and to locate the window of implantation. This symptothermal method is one of the very safe family planning methods with a method failure of 0.4 (Pearl Index) and is the only comprehensively evidence-based version of all natural behavioural methods [5].

Important aspects contributing to the relatively high safety are the meticulous documentation of the cycle-dependent symptoms of self-observation, the correct application of the method (e.g., calculation rules) and the exact quotation of disturbances or, more general, disorders in the cycle so that if necessary, disturbed temperature measurements can be taken into account in the cycle analysis. The users of the symptothermal method of family planning (Sensiplan®) know a catalogue of potential disturbances interfering with the interpretation of their basal body temperature curves and cervical mucus signs to determine the fertile window, as this is part of the extended set of rules. Those users who have provided cycles for scientific evaluation indicated in advance whether there was the intention to conceive in the current cycle and whether each sexual intercourse was registered. The cycle analysis with determination of the first and last fertile days was carried out by both the user and specially trained project staff. The latter also determined the time of ovulation as so-called clinical ovulation according to a definition previously published [3]. This ensured reliable determination of the follicular phase length, ovulation day, luteal phase length and location of the implantation window with highest implantation probability on the 5th–9th postovulatory days in the cycle [3, 6]. In case of a temperature elevation of 16 days or more, a pregnancy was assumed and a confirmation of the clinical pregnancy and its outcome was subsequently actively obtained from the user.

[1] Best definition: Bundesmantelvertrag-Ärzte der Kassenärztlichen Bundesvereinigung, Appendix 28, §4, of 2017.

The current cycle database is managed with Microsoft Access®. The nature of the data collection is prospective. Well over 100 plausibility checks and cross checks ensure a nearly error-free entry of the data. For this study, all pregnancy cycles were consulted first. From a total of 504 prospectively collected cycles series, which finally ended in a clinical pregnancy, all series in which time to pregnancy took more than 13 cycles (including the conception cycle) were excluded, since in these cases, a relevant subfertility of the couple must be assumed [7, 8]. All series in which clinical ovulation could not be determined in the conception cycle and in the last three pre-cycles, or sexual intercourse was not fully registered were excluded. In total, 237 cycle cycles of 237 subjects were included in the analysis. In addition to the conception cycle, if available, the three preceding cycles and all respective questionnaires were examined in the original sheets regarding the presence and quality of disturbances ($n=747$ cycle data sheets, $n=237$ participant questionnaires and $n=237$ drop out questionnaires) and catalogued in appropriate tables in Microsoft Excel®. In fact, up to five pre-cycles were initially examined and catalogued. However, due to very small numbers, a restriction had to be made to three pre-cycles, since most of the conceptions occurred within three cycles, which coincides with own previous results (see Fig. 2b) [9].

Figure 1 shows the flowchart of included and excluded subjects. The 237 subjects with fully documented conception cycles and up to three fully documented pre-cycles in a row were divided into a study group ($n=145$, with disturbances in the conception cycle) and a control group ($n=92$, no disturbances in the conception cycle) to determine the influence of disturbances in conception cycles in the comparison with existing pre-cycles and identify possible differences (number of cycles up to pregnancy) between women with finally undisturbed conception and women with impaired conception.

The subjects recorded all special features and potential disturbances in the cycle data sheet, which could often be validated with disturbed temperature measurements and were classified by scientific panel decision as follows:

(1) Diseases[2] and/or pain at the time of ovulation, including, e.g., common fever colds, headaches, sore throat, cystitis, migraine, flu, unclear abdominal pain, gastrointestinal problems/infections, back pain. Most often, colds, headache, throat and limb pain were indicated. The so-called ovulation pain was given in the cycle data sheets, but explicitly not taken into account in this analysis.
(2) Stress factors at the time of ovulation; explicitly indicated as, for example, on-call service, house building, move, death of a beloved animal or pet, night shift, disturbing insomnia. Only negative stressors were considered. From this, if explicitly stated by the user, relaxing events around the time of ovulation (e.g., holiday, weekend trip) were delineated.
(3) Diseases during the suspected implantation phase, e.g., fever, colds, sore throat, headache, gastrointestinal infections. These were also explicitly stated on the cycle log.
(4) Stress during the suspected implantation phase, e.g., stressful travel, sick child, little sleep, night duties. Of these, even if explicitly stated by the user, the relaxing events were delineated around the presumed implantation time (e.g., holidays, celebrations).
(5) Sexual intercourse as a possible disturbance factor in the suspected implantation phase.
(6) Other "disturbances", such as diets, visits to the hospital, partnership problems, dentist treatments. This category was not taken into account in all analyses, as factors were subsumed below which are not safe to be considered as possible "disturbances".

By far the most common disturbances were (in decreasing order) common colds (46%), pain (27%) (head, neck, bladder, abdominal) and stress (22%).

In addition, the following cumulative categories were formed to identify possible addition effects:

- Disturbances around suspected ovulation ((1) and (2)).
- Disorders during the suspected implantation phase ((3),(4) and (5)).
- Total disturbances (includes disturbances related to both the suspected ovulation and the suspected implantation phase).

Statistics

The data analysis was carried out with Microsoft Excel® and the open source statistics package R.[3] To exclude subfertility, only subjects who became pregnant within 13 cycles were included in the analysis. Therefore, the conditional probability of pregnancy could not be determined directly depending on existing or missing disturbances. However, it was possible to investigate as an intraindividual comparison whether disturbances or relaxation factors have occurred more or less frequently in the last three pre-cycles than in the

[2] Serious diseases that would have required further medical diagnosis and/or therapy were not present. Corresponding cycle series would have been excluded. In this case, diseases refer to so called minor diseases (see footnote 1).

[3] R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/.

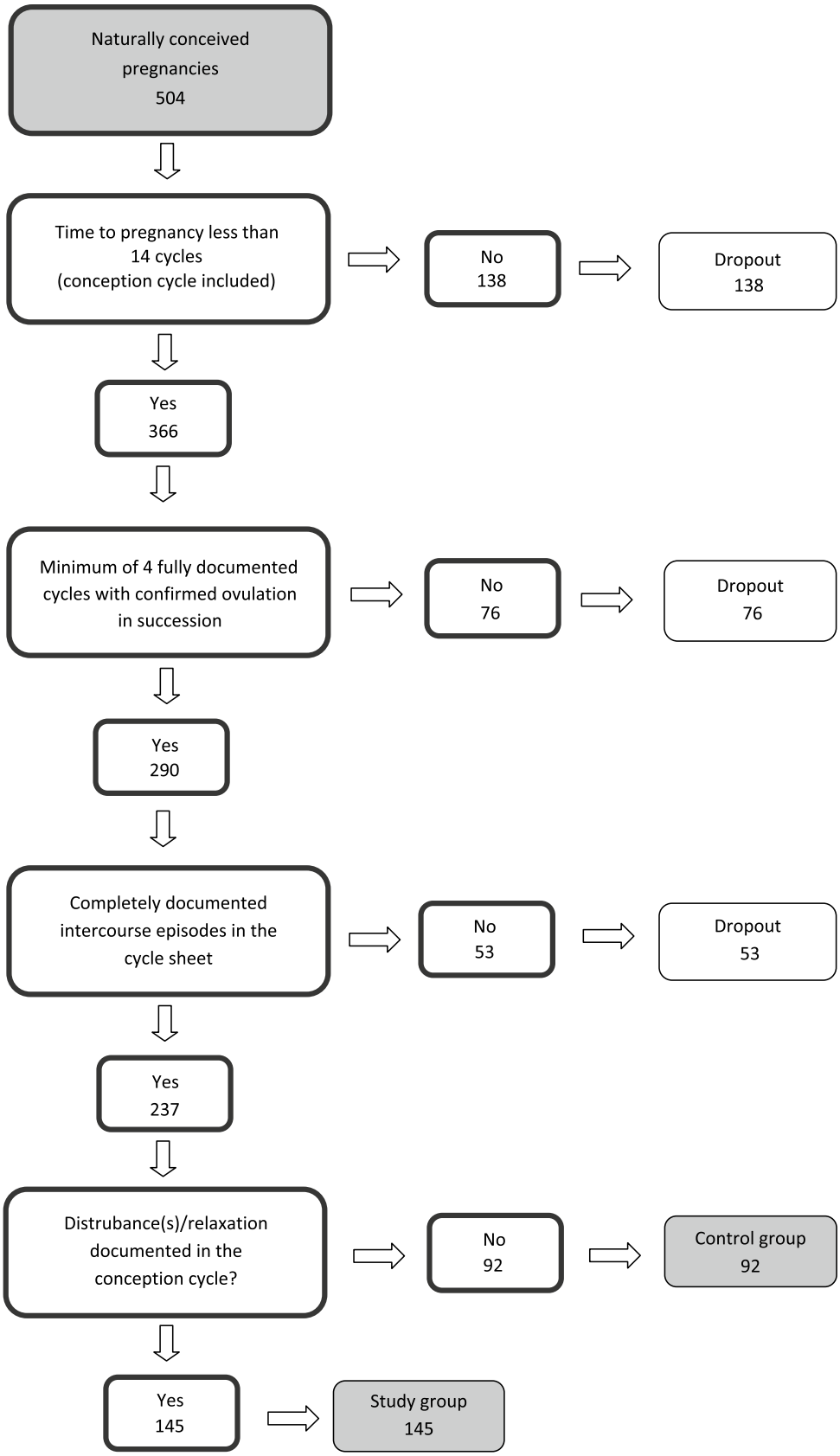

Fig. 1 Flowchart of the selection of subjects

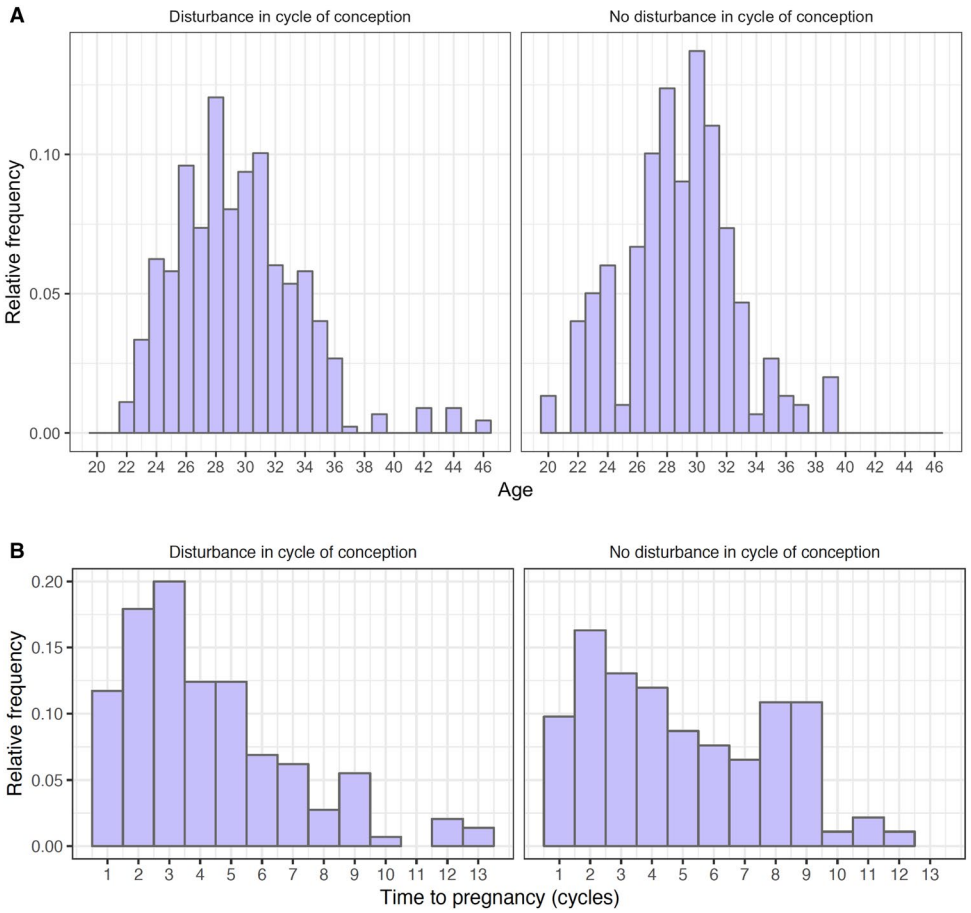

Fig. 2 **a** Age distribution of women in the study and control group, *Y* axis: relative frequency; *X* axis: age. The average age of female subjects is 29.15 years (95% CI 21.29–37.01), 29.39 (95% CI 21.03–37.75) years in the study group and 28.76 (95% CI 21.30–36.22) in the control group. **b** Number of cycles to pregnancy in the study and control group, *Y* axis: relative frequency; *X* axis: number of cycles to pregnancy. More than half of all conceptions occurred in the first three cycles in the study group and for the control group in the first five cycles

conception cycle. For this purpose, a logistical mixed regression model has been adapted for each interference factor and the relaxation factors, which predicts the probability of the occurrence of the corresponding factor based on the cycle number (conception cycle or pre-cycles 1–3). These models included a random and a fixed effect for the axis section in the regression equation and a fixed effect per pre-cycle, with the conception cycle itself being the reference category. Due to the accidental effect, it was taken into account that several correlated observations, probably unobserved and of different nature, per subject were included in the analysis. It was also allowed that each subject could have noted differently many disturbances, e.g., due to different sensations of stress or pain. A negative fixed effect for a pre-cycle means a lower occurrence; a positive effect means a more frequent occurrence of the disturbance or relaxation factor compared to the conception cycle. Using one-sided simultaneous Intersection–Union Wald tests,[4] the null-hypotheses were investigated that disturbance factors occur in at least one pre-cycle at least as frequently and relaxation occurs in at least one pre-cycle at most as frequently as in the conception cycle, and the associated one-sided 95% confidence intervals were calculated. A significant test result means that a disturbance factor normally regarded as negative occurs more frequently in the conception cycle, or that relaxation usually regarded as positive occurs less frequently in the conception cycle than in all three pre-cycles.

Because intraindividual changes were observed with a time-to-event outcome (conception), the effects of disturbances and relaxation on the time to pregnancy (TTP) were analysed. For each disturbance and relaxation factor, cumulative pregnancy rates were initially estimated using an extended Kaplan–Meier method, [5,6] [10]. In this time-dependent, cycle-based case–control analysis, the subjects

[4] R package multcomp, Torsten Hothorn, Frank Bretz and Peter Westfall (2008). Simultaneous inference in general parametric models. Biometrical Journal 50 (3), 346–363. URL: https://cran.r-project.org/web/packages/multcomp/vignettes/generalsiminf.pdf.

[5] Edward L. and Paul Meier (1958). Nonparametric estimation from incomplete observations. Journal of the American statistical association 53 (282), pp 457–481. URL: http://www.jstor.org/stable/2281868
R package survival, Therneau T (2015). A Package for Survival Analysis in S. version 2.38.
https://CRAN.R-project.org/packagesurvival).

[6] Steven M Snapinn, Qi Jiang, Boris Iglewicz (2005). Illustrating the Impact of a Time-Varying Covariate With an Extended Kaplan–Meier Estimator, The American Statistician, 59:4, 301–307, https://

repeatedly change the status of their group membership (cycle with disturbance factor/relaxation, cycle without disturbance factor/relaxation).

To analyse the impact of disturbances and relaxation for statistical significance, a Cox regression[7] was performed for each factor taking into account the number and timing of events. The age of the participants was included as an additional factor for adjustment procedures. The hazard ratio of conception probabilities was calculated for each factor of disturbance separately. A hazard ratio greater than 1 means that the occurrence of the disturbance/relaxation increases the probability of conception. Using one-sided Wald tests, the zero hypotheses were investigated that the disturbing hazard ratios are at least 1 and the relaxation hazard ratios are at most 1, and the associated one-sided 95% confidence intervals were calculated. A significant test result means that the disturbance in question increases or relaxation reduces the probability of conception.

Results

All conception cycles with less than 13 ovulatory pre-cycles in uninterrupted succession with the intention of a pregnancy were analysed with regard to the documentation of disturbances and relaxation factors. There were significantly more conception cycles with disturbances than without (61%, $n=145$, study group vs. 39%, $n=92$, control group, Fig. 1). Relaxation factors alone or in cycles with disturbances were given in 11% ($n=79$).

The average age of the female subjects is 29.15 years (95% CI 21.29–37.01), 29.39 years in the study group (95% CI 21.03–37.75) and 28.76 years in the control group (95% CI 21.30–36.22). Figure 2a shows the age distribution. Study group and control group do not differ significantly in age.

In both groups, up to three consecutive pre-cycles were included in the statistical analysis, since numbers of more than three pre-cycles became too low due to the rapid occurrence of the desired conceptions with ovulation focused intercourse. Figure 3 shows the relative frequency for disturbances in the conception cycle, as well as for a maximum of three pre-cycles. By definition, the conception cycle itself is disturbance free in the control group. Disturbances in the conception cycles of the study group are much more common compared to the respective pre-cycles of this group. The Wald test for statistical significance for the 5% level of these observations for all subjects shows that diseases/pain and stress around ovulation occur statistically significantly more frequently in the conception cycles compared to the pre-cycles (Fig. 4). Sexual intercourse and stress in the implantation phase occur significantly more frequently in the conception cycles compared to the first pre-cycle, i.e., do not interfere with the implantation process but even increase the chance of conception. Relaxation phases around ovulation and in the suspected implantation phase do not have a statistically significant positive effect, and so do not bring any advantage in terms of conception chances. Overall, the occurrence of disturbances in the conception cycle is coupled with a significantly higher prospect of pregnancy.

Since in the pre-cycles of the study group, frequent disturbances occur both at the time of ovulation and in the suspected implantation window compared to the control group, and the number of cycles up to pregnancy in the study group is lower (Fig. 2b), a time-dependent, cycle-based case–control analysis according to Kaplan–Meier, in which the participants repeatedly change the status of their group membership (cycle with disturbances, cycle without disturbances) was added. The analysis was carried out for the conception cycle and its three pre-cycles. It turns out that for all disturbances, the probability of pregnancy increases and that women with disturbances in cycles with the desire for children have become pregnant more quickly in our study (Fig. 5). These results are statistically significant ($p \leq 0.05$) for diseases/pain and stress at ovulation. Sexual intercourse and stress in the suspected period of implantation in cycles with desire for children are also associated with a significantly higher probability of pregnancy (Fig. 6). In case of minor diseases, pain and fever during the implantation phase, only a tendency to positive effect is observed, but is not statistically significant. Relaxation at the time of ovulation or during the suspected implantation period has no representable effect.

Only one spontaneous miscarriage was documented in both groups and no heterotopic pregnancies by active follow-up for confirmation of an ongoing pregnancy. This incidence is probably underrepresented. There is no information on live birth rates. By passive follow-up, there seems to be no evidence of more frequent pathological course of pregnancy in the study group compared to the control group.

Discussion

To our knowledge, this study is the first systematic and scientific evaluation on questions of the impact of disturbances in natural conception cycles and their respective

Footnote 6 (continued)

doi.org/10.1198/000313005X70371; Terry Therneau, Cindy Crowson, Elizabeth Atkinson. Using Time Dependent Covariates and Time Dependent Coefficients in the Cox Model (2013). URL: https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf.

[7] D. R. Cox (1972). Regression models and life-tables. Journal of the Royal Statistical Society. Series B (Methodological) Vol. 34, No. 2, p 187–220.
http://www.jstor.org/stable/2985181.

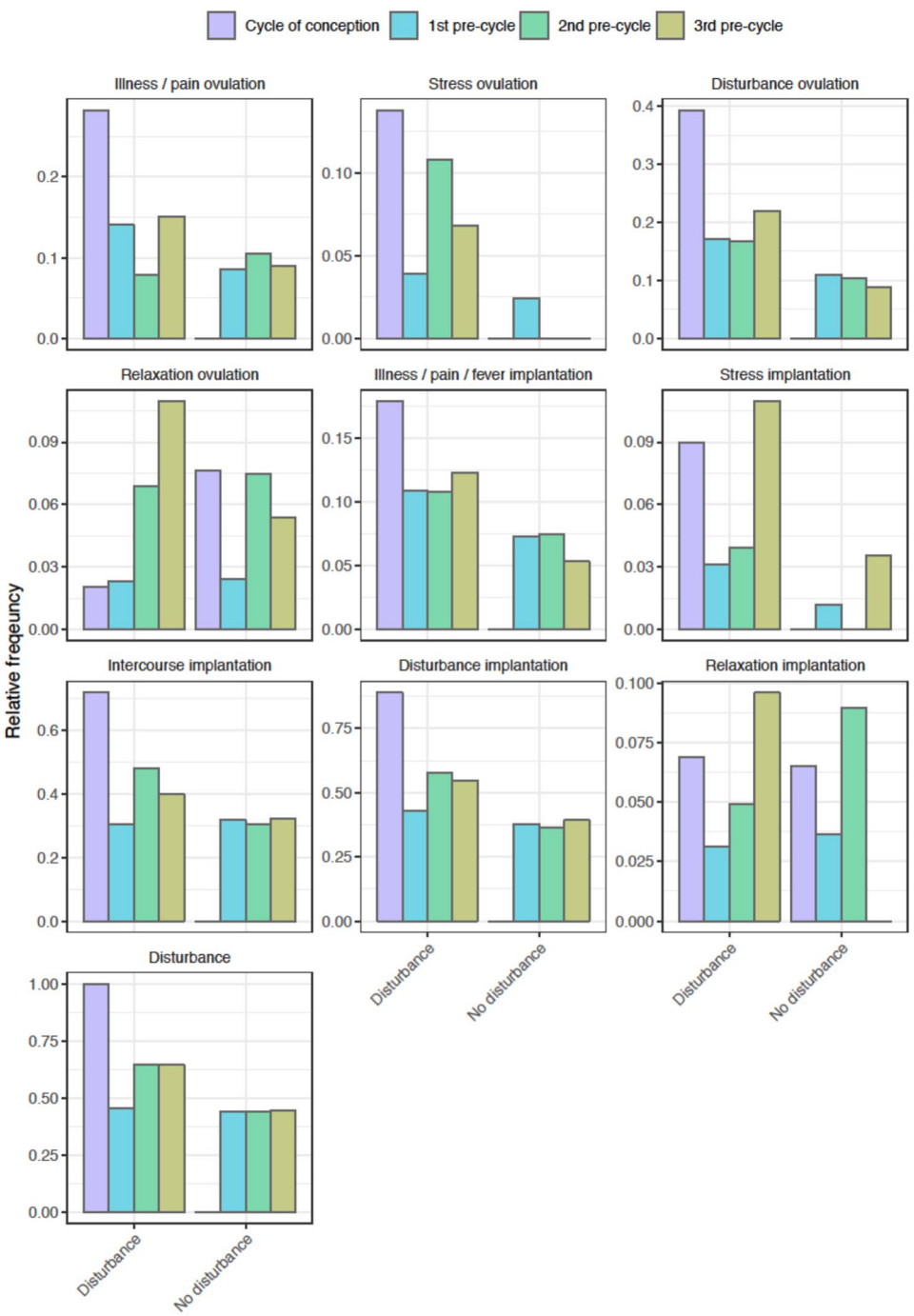

Fig. 3 Relative frequency of disturbances and relaxation states in the conception cycle and in the three pre-cycles for the study (disturbance) and control group (no disturbance)

pre-cycles. Contrary to expectations and general assumptions, disturbances have no negative effects—on the contrary. The often recommended relaxation does not have a positive effect, contrary to expectations.

In detail, it is evident that disturbances such as minor diseases, stress or sexual intercourse during the suspected window of implantation in conception cycles certainly do not reduce the chance of clinical pregnancy—on the contrary, the probability of pregnancy increases significantly by a factor of 1.32 (95% CI 1.04–1.70) and women with disturbances in cycles with the desire to infant become pregnant faster. A view on the strength of the effects reveals that effects in favour of conception are more pronounced when occurring around ovulation. Relaxation states at the time of ovulation and/or during the suspected implantation period have no representable positive effect on the probability of a pregnancy.

Why could disturbances at the time of ovulation favour the prospect of pregnancy? Here, immunological

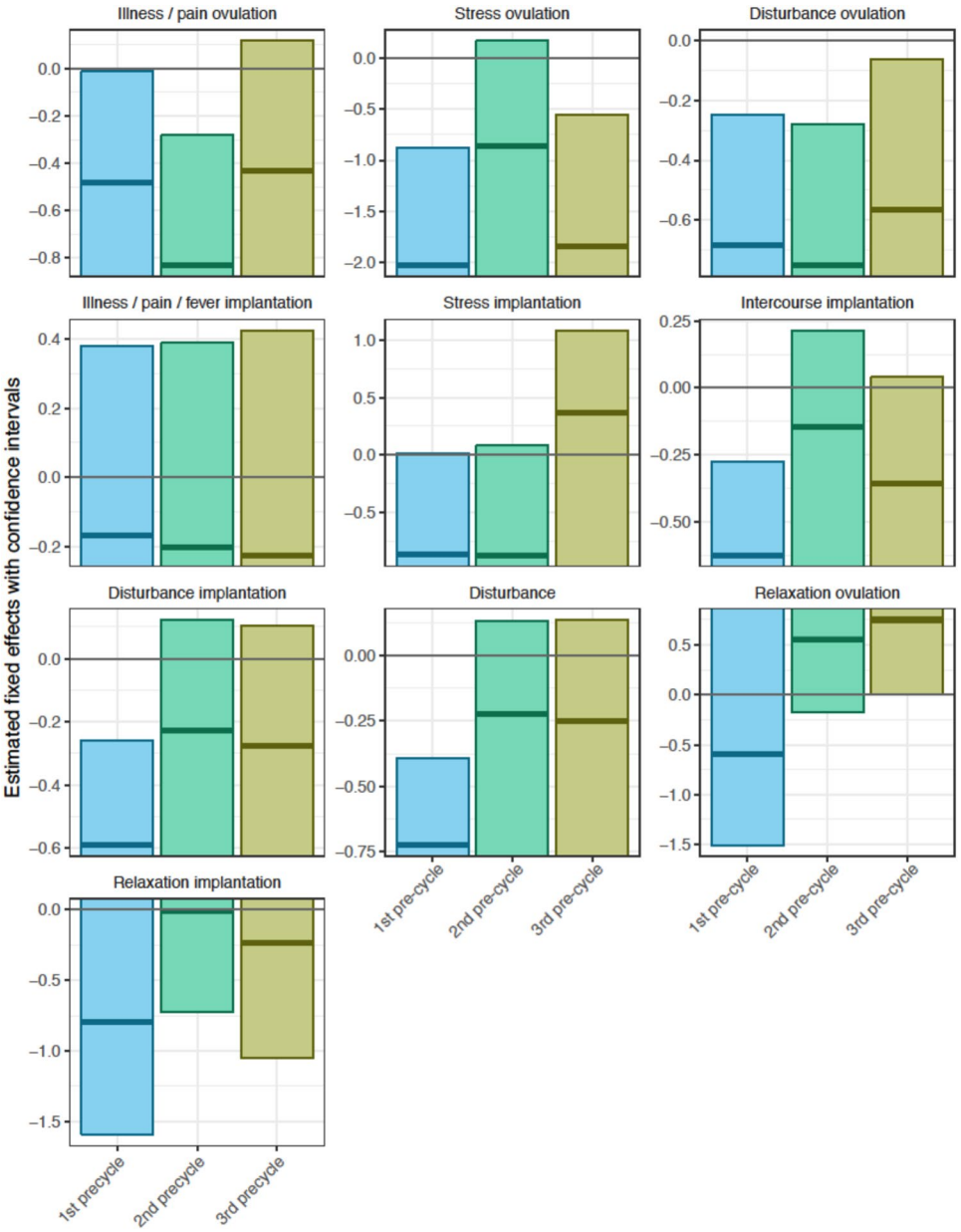

Fig. 4 Estimated fixed effects (cross lines) of the last three pre-conception cycles with one-sided simultaneous intersection–union confidence intervals to 95% level (bars). If the upper end of a bar does not exceed the "0", this disturbance occurs significantly less frequently in the respective pre-cycle than in the actual conception cycle. "Ovulation disturbance" and "Implantation disturbance" summarise the preceding partial graphs. In case of disturbance overall, all faults in the conception cycle were cumulated. Especially with disturbances around ovulation, the probability of conception is significantly higher. With sexual intercourse in the implantation period, the prospect of pregnancy is significantly higher in comparison with the first pre-cycle. Thus, in the implantation phase, sexual intercourse is not generally disadvantageous. Relaxation phases around ovulation or implantation have no representable effects, so does not bring measurable benefits

considerations come into play, since in this study, the most common disturbances have been colds, pain and stress.

The scientific data on immunological processes around the implantation phase are currently confusing and there is no uniform concept [11]. However, we know that with ovulation, the cell populations of immunocompetent cells in the luteal (and decidual) endometrium change significantly [12]. Postovulatory $CD56^{bright}$ +/CD16- uterine killer cells (uNK) predominate. It may be assumed that immune system-activating disturbances increase immune tolerance to the semiallogenic embryo in the sense of immunological distraction [13] or, together with frequent periovulatory sexual intercourse, immunological conditioning of the endometrium is promoted [11, 14]; thus, with each menstrual period, the possibility of new immunological conditioning in the upcoming cycle is given.

Steiner et al. [15] conducted a prospective study in 2014 to assess whether sexual intercourse in the implantation phase of natural cycles is disruptive or beneficial to the onset of pregnancy. 564 women aged 30–44 years with 1332 cycles were examined. As a result, sexual intercourse during the implantation period led to a reduced probability of conception, depending on the number of days on which sexual intercourse was performed. This result is in contradiction with our findings. However, our study did not count the intercourse episodes during the implantation phase. Up to three intercourses took place during the suspected implantation period. Therefore, whether very frequent sexual

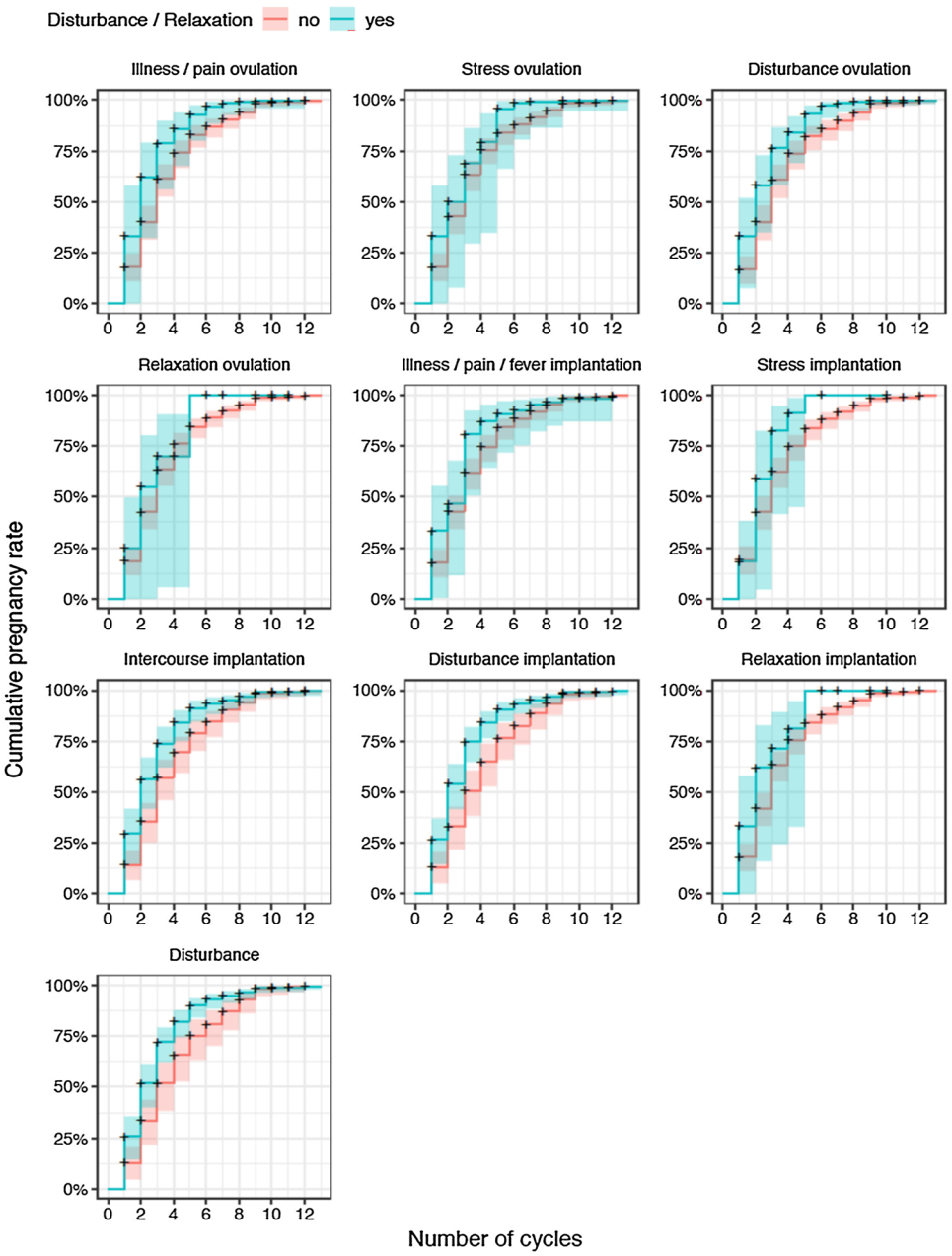

Fig. 5 Cumulative pregnancy probabilities (TTP) according to Kaplan–Meier with 95% confidence intervals. Since the analysis included only cycle courses in which finally a pregnancy occurred within 13 cycles, Kaplan–Meier curves achieve a probability of pregnancy at 13 cycles of 100%. It turns out that for all disturbances in cycles with the desire for children, the probability of conception increases, and women with disorders in cycles with the desire to have children become pregnant significantly faster (see Fig. 6). With relaxation at the time of ovulation, respectively, in the suspected implantation period, conception does not occur faster. Because of the overlap of confidence intervals, the statistical significance was tested using a Cox regression model (Fig. 6)

intercourse, perhaps due to frequent and severe uterine contractions, can have negative effects in some cases, must remain open, since Steiner et al. have only considered this potential disturbance factor in isolation and conceivable confounders have not been considered in the patient selection. Interestingly, the question of the effects of sexual intercourse in the implantation window for IVF cycles was investigated in a study of Tremellen et al. with 478 IVF cycles and a total transfer of 1343 embryos [16]. Two groups, with and without sexual intercourse after embryo transfer, were compared. There was no significant difference in the probability of pregnancy. But the likelihood of successful early embryo implantation was significantly higher in women with sexual intercourse after embryo transfer compared to those who abstained (11.01 versus 7.69 viable embryos per 100 transferred embryos, odds ratio 1.48, 95% confidence interval 1.01–2.19).The authors conclude that contact with seminal fluid and the following immunological reaction could be the cause of this difference. This has led to appropriate clinical use in the form of intravaginal injection of homologous seminal plasma at the time of oocyte retrieval or embryo transfer [17, 18].

Stress as a disturbing factor of conception is also discussed very controversially [19–21]. Akther et al. found

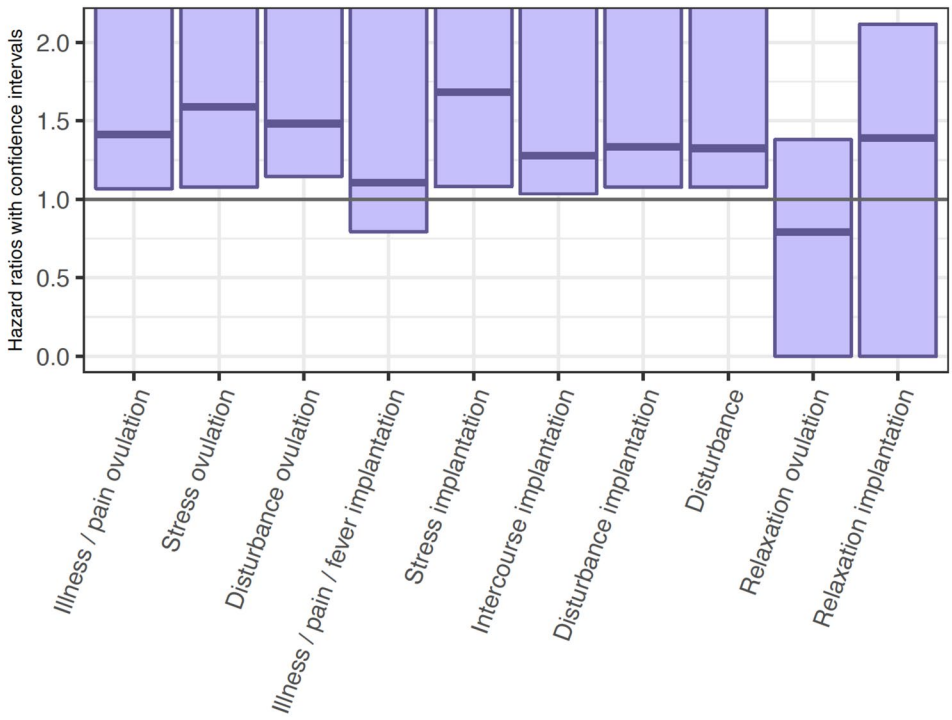

Fig. 6 Hazard ratios (cross lines) with 95% unilateral confidence intervals (bars): Hazard ratios indicate by which factor the probability chance of pregnancy is increased when there is no disturbance factor. If the lower end of the beam falls below 1, the disturbance factor has no significant influence. Disturbance factors at the time of ovulation are associated with a higher probability of pregnancy, i.e., faster onset of pregnancy. Sexual intercourse and stress in the suspected window period of implantation in cycles with desire for children are also associated with a significantly faster occurrence of spontaneous conception. Other possible disturbances (minor diseases, pain, fever) do not show statistically show a significant positive effect. Relaxation periods at the time of ovulation, respectively, in the suspected implantation period, do not have a significant effect

reduced chances for spontaneous conception for periovulatory stress [21]. This is quite conceivable for severe stress, as the hypothalamic–hypophyseal axis is disturbed and ovulations can be absent or shifted [22]. In this study, we have only been able to investigate subjectively perceived "normal" everyday stress, which according to the evaluations of the temperature curves did not disturb the ovulation process. With stress in the luteal phase, the chances of conception increased, which could fit the immunological explanations of our observations. In the presence of stressors leading to objectifiable, physical stress reactions (increase in cortisol, increased amylase activity in saliva), there are studies that found a reduced spontaneous conception and IVF pregnancy rate [23–25].

In IVF cycles, subjectively perceived emotional stress after a meta-analysis by Boivin in terms of success does not matter because, according to the authors, the hypothalamic–pituitary axis is controlled from the outside (controlled ovarian stimulation) [26]. Bihde criticises, therefore, that the concern that stress could harm causes particularly severe stress and psychological stress [27]. Appropriate psychological interventions for stress reduction in fertility therapy could not prove in corresponding studies that the chances of success increase [28, 29]; however, patients felt more comfortable, which is of course a valuable advantage [30]. The fact that subjectively perceived stress in natural conception cycles even increases the chances or relaxation does not bring benefits has not been scientifically shown before to our knowledge.

Analogue immunological considerations have led to current, prospective studies in reproductive medicine in which patients are vaccinated against influenza before an IVF cycle to promote the chances of implantation in the pre-cycle (https://clinicaltrials.gov/ct2/show/NCT02947217). The results are still pending.

It is one of the strengths of this register study that it could be carried out on a collective of provenly fertile women. A comparison with women who did not become pregnant would not have been possible, since there could have been subfertility and the causes of effects would have remained unclear. However, whether the effects described here also apply to a subfertile collective must remain open. It is conceivable that disturbances not only may aggravate subfertility but also may be beneficial.

The meticulous processing of a large number ($n = 747$) of original cycles of natural family planning is another

strength; it is precisely the documentation of exceptional disturbances that is part of the extended control system of the symptothermal method Sensiplan® and, therefore, a documentation bias is low, since not every everyday detail was noted. Another strength is the use of statistical methods for which the variables (disturbances) to be investigated are not dependent on the inevitable heterogeneity (random, observed and/or unobserved effects). Similar studies are not known to the authors. A weakness of the study is that the studied disturbances have not been or could not be quantified (e.g., application of pain or stress scales, number of sexual intercourse) and thus the entries in the cycle data sheet are subjective. However, this subjectivity reflects the reality of questions and consultations. In addition, intra-individual comparisons (conception cycle and pre-cycles of the same woman) were carried out in the statistical analyses of this study, so that subjective colouring (tendency to aggravation or trivialisation of disturbances) is removed. The relevance of recorded disturbances was also assessed on the basis of the effects on basal temperature values, which in many cases showed "disturbed" measurements. According to the Sensiplan® method, such disturbed values are not used later to detect the temperature rise. Another possible weakness is that all disturbances and relaxation factors were considered independently of each other, without systematically taking into account possible interactions (e.g., lifting effects when relaxation phases and disturbing factors around ovulation occur simultaneously). However, the numbers for the various possible combinations were too small for in-depth interaction analyses. Addition effects have been recorded with the formation of cumulative categories. Eliminating effects are not expected, since disturbing factors are not detrimental and relaxation alone is without effect.

The results of this study help to relieve couples wishing to have children of unsustainable recommendations and advice and to inform them that disturbances such as trifle diseases and stress in conception cycles are not detrimental. Although further studies on these questions are necessary, this study gives first, perhaps some preliminary answers. This deprives couples of the guilt of doing something wrong in cycles without the desired pregnancy. But doctors are also relieved and even strengthened by not having to give their advice following general assumptions, but by being able to rely on scientific research and thereby contribute to stress reduction.

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Author contributions CG: main author, research idea, study design, statistical analysis, writing of the manuscript. A-KK: data recording, data analysis, writing of the manuscript. JS: statistical analysis, writing of the R progam codes. SH: research idea, data recording. PM: writing of the manuscript. GF: research idea, study design, writing of the manuscript. TS: study design, writing of the manuscript

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Compliance with ethical standards

Conflict of interest Christian Gnoth is a principal investigator of clinical trials for the development and evaluation of fertility monitors and receives support from SPD Development Company, Bedfort, UK. No conflicts of interest of the other authors.

Ethical approval Ethical approval was obtained by the Section of Natural Fertility of the German Society of Gynecological Endocrinology and Fertility Medicine at the University of Heidelberg. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki of 1964 and its later amendments.

Informed consent All participants have signed informed consents and agreed in using their anonymized data for scientific purposes. All participants were free to withdraw at any time.

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