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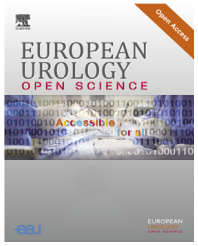

European Association of Urology

Prostate Cancer

Magnetic Resonance Imaging–targeted Prostate Biopsy Compared with Systematic Prostate Biopsy in Biopsy-naïve Patients with Suspected Prostate Cancer

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Abstract

Background: It remains uncertain whether transrectal ultrasound (TRUS)-guided systematic biopsies can be omitted and rely solely on multiparametric magnetic resonance imaging–targeted biopsies (MRI-TBx) in biopsy-naïve men suspected of prostate cancer (PCa).
Objective: To compare PCa detection in biopsy-naïve men between systematic biopsy and MRI-TBx.
Design, setting, and participants: A prospective cohort study was conducted in a Dutch teaching hospital. Consecutive patients with suspected PCa, no history of biopsy, and no clinical suspicion of metastasis underwent both TRUS-guided systematic biopsies and MRI-TBx by multiparametric magnetic resonance imaging (mpMRI)-ultrasound fusion, including sham biopsies in case of negative mpMRI.
Outcome measurements and statistical analysis: Clinically significant PCa (csPCa), defined as group $\geq$2 on the International Society of Urological Pathology grading, was detected.
Results and limitations: The overall prevalence of csPCa, irrespective of biopsy technique, was 37.4% (132/353) in our population. MRI-TBx were performed in 263/353 (74.5%) patients with suspicious mpMRI (Prostate Imaging Reporting and Data System [PI-RADS] $\geq$3). The detection rates for csPCa were 39.5% for MRI-TBx and 42.9% for systematic biopsies. The added values, defined as the additional percentages of patients with csPCa detected by adding one biopsy technique, were 8.7% for the systematic biopsies and 5.3% for MRI-TBx. In patients with nonsuspicious mpMRI, five cases (6%) of csPCa were found by systematic biopsies.

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Conclusions: This study in biopsy-naïve patients suspected for PCa showed that systematic biopsies have added value to MRI-TBx alone in patients with mpMRI PI-RADS >2.

Patient summary: We studied magnetic resonance imaging (MRI)-guided prostate biopsy for diagnosing prostate cancer and compared it with the standard method of prostate biopsy. Standard systematic biopsies cannot be omitted in patients with suspicious MRI, as they add to the detection of significant prostate cancer.

1. Introduction

The use of multiparametric magnetic resonance imaging (mpMRI) combined with magnetic resonance imaging–targeted biopsies (MRI-TBx) aims to provide a less invasive and more accurate diagnostic approach in prostate cancer (PCa) [1]. MRI-TBx potentially reduce the number of unnecessary biopsies, resulting in fewer clinically insignificant cancers being detected and an improved detection of clinically significant PCa (csPCa), defined as International Society of Urological Pathology (ISUP) grade ≥2 [2–4]. Several high-impact studies (level I evidence) have used different approaches and inclusion criteria to address the issue of how to manage biopsy-naïve patients suspected for PCa. The overall conclusion is that MRI-TBx improve the detection of csPCa, but that systematic biopsies cannot be omitted because the combination of the two techniques adds significant value [3,5]. The risk of MRI-TBx failure in up to 8.8–17% of cases and the risk of significant ISUP upgrading in up to 8.7% of cases lead to diagnostic uncertainty [5,6].

The so-called MRI pathway (ie, mpMRI combined with MRI-TBx without systematic biopsy or when mpMRI is negative no biopsy at all) relies heavily not only on the accuracy of MRI-TBx, but also on mpMRI detection and interpretation. The 4M study indicated that the number of suspicious lesions can be downgraded when the level of mpMRI expertise is high, which can prevent biopsy in 57% of men [4]. However, interpretation of mpMRI results by radiologists is notorious for its large, experience-dependent, interobserver variability [7]. This knowledge led to the most recent recommendation to combine MRI-TBx with systematic biopsies in biopsy-naïve patients suspected for PCa on mpMRI [8]. Despite growing evidence in favor of the MRI pathway, clinicians are still failing to implement it in the clinical setting because of continued debate on whether systematic biopsy can be omitted [9,10].

In this prospective cohort study, biopsy-naïve patients with suspected PCa underwent mpMRI, and both systematic biopsies and MRI-TBx were performed in all patients. In case of negative mpMRI, systematic biopsies as well as sham biopsies were taken to investigate the number of missed cases of csPCa and to blind pathologic analyses respectively. The primary outcome of the study is the detection rate of csPCa comparing systematic biopsies with MRI-TBx in all patients.

2. Patients and methods

2.1. Trial design

We conducted a prospective cohort study in a nonacademic teaching hospital in Zwolle, the Netherlands, between February 2018 and September 2020, after receiving approval from our institutional ethics review board (NL63640.075.17). The protocol has been registered in the Dutch Trial Register (NL7019), and all participants gave written informed consent. The study was funded by the Institutional Scientific Innovation Fund of Isala Clinics with no input from any commercial entity.

2.2. Participants

Consecutive biopsy-naïve patients with no prior history of PCa were invited to participate by their urologist when first visiting the outpatient clinic. Patients were eligible for the study if there was a suspicion of PCa because of an elevated prostate-specific antigen (PSA) level of ≥4 ng/ml and/or a suspicious digital rectal examination (DRE). The exclusion criteria were PSA >20 ng/ml, age <18 yr, clinical suspicion of bone metastases, and/or contraindication for mpMRI.

2.3. Magnetic resonance imaging

A 3-T scanner with a phased-array body coil was used for mpMRI. Axial T1-weighted and triplanar T2-weighted (T2W), diffusion-weighted (b0, 50, 800, 1500, ADC, and B2000), and dynamic contrast-enhanced imaging were performed, with hyoscine butylbromide administered before the examination to reduce bowel motion. Images were evaluated by one of two radiologists (M.V.V. or E.D.B., both with >8 yr of experience in prostate MRI evaluation) using the Prostate Imaging Reporting and Data System (PI-RADS), version 2.

2.4. mpMRI-ultrasound fusion and biopsy

Axial T2-weighted images were prepared for the mpMRI-ultrasound fusion biopsy procedure using the MIM Symphony DX software (Cleveland, OH, USA). Lesions with PI-RADS scores ≥3 were marked by the radiologist. However, if more than two areas were suggestive of PCa, only the two with the highest PI-RADS scores were marked.

Biopsies were taken within 4 weeks after mpMRI, using a BK3000 ultrasound scanner and a prostate triplane transducer (BK Ultrasound, Herlev, Denmark). Two operators (N.G.A. and F.J.S.H., each with >1 yr of experience in systematic prostate biopsies) performed all biopsy procedures after extensive proctor instruction and training. The operator was blinded to the mpMRI findings at the start of the biopsy procedure. In total, ten systematic prostate biopsies were obtained from both sides of the prostate, according to international guidelines, with ultrasound and DRE used for guidance [8]. Right and left cores were stored separately in formalin. At the same time, without removing the ultrasound

probe, we used the MIM software to fuse the mpMRI images and marked regions (if applicable) with the ultrasound images. After adequate fusion, a maximum of two biopsies were taken from each marked region. If no PCa was suspected on mpMRI, a small dot was marked on the fused image to provide a negative control for the operator and two sham biopsies were taken randomly from the prostate. The additional biopsies were potted separately in formalin for each suspicious region. This provided a maximum of 12–14 biopsies per participant.

2.5. Histopathology

Biopsies were reviewed by pathologists specializing in urology who were not blinded to clinical data (eg, PSA or DRE findings), but who were blinded to the mpMRI findings and additional biopsy type (ie, target or sham). Tissue was processed, reviewed, and reported according to the most recent updated Gleason grading system [11]. In the final pathology report, the number of positive biopsy cores, length of tumor per positive core, and tumor percentage were noted, next to the Gleason score and tumor characteristics such as the absence or presence of perineural growth or extraprostatic extension.

2.6. Definition of clinical significance

We defined clinical significance based on the Gleason score and corresponding ISUP group, such that csPCa had a Gleason score of 3 + 4 or higher (ISUP ≥2) and non-csPCa had a Gleason score of 3 + 3 (ISUP 1) [8].

2.7. Statistical analysis

Sufficient level of power was based on assumed sensitivity of at least 90% for the detection of all PCa by using MRI-TBx in comparison with systematic biopsies. For a confidence interval (CI) of 5%, an alpha of 95%, and an assumed PCa prevalence of 40% in the target population, 346 men needed to be included, which we increased to 353 participants to account for protocol deviations. Excluded or withdrawn participants were replaced by new participants where possible.

The primary outcome of the study is the detection rate of csPCa comparing systematic biopsies with MRI-TBx in all patients. Additionally, we calculated the sensitivity and specificity of mpMRI and MRI-TBx combined, using systematic biopsies as a control. Lastly, we analyzed the added value of MRI-TBx and systematic biopsies, and the agreement between the two modalities.

Baseline characteristics were assessed for normality using the Shapiro-Wilk test. We estimated the sensitivity and specificity of mpMRI and MRI-TBx combined for detecting csPCa, using systematic biopsies as the gold standard for comparison. Given the priority of detecting csPCa, we assessed the negative predictive value of mpMRI and MRI-TBx combined in the absence of systematic biopsies. We included 95% CIs, as appropriate. All data were analyzed by IBM SPSS Version 25 (IBM Corp., Armonk, NY, USA).

Any adverse events occurring between inclusion and 2 weeks after biopsy were documented according to the Medical Research Involving Human Subjects Act (WMO). Additionally, serious adverse events (eg, hospital admittance, life-threatening illness, or death) were reported to the institutional ethics review board and the Central Committee on Research Involving Human Subjects.

3. Results

We assessed 411 men for eligibility and excluded 35 before mpMRI and 23 after mpMRI, resulting in 353 being recruited for the final analysis (Fig. 1). Patient characteristics are presented in Table 1; in total, 90 (25.5%) patients had a PI-RADS score of ≤2 on mpMRI and 263 (74.5%) patients had at least one PI-RADS ≥3 lesion (351 lesions in total). There were 13 (3.7%) serious adverse events during the study, the details of which are included in Supplementary Table 1. All patients recovered fully.

The overall prevalence of csPCa, irrespective of biopsy technique, was 37.4% (132/353) in our population (Table 2). MRI-TBx were performed in 263/353 (74.5%) patients

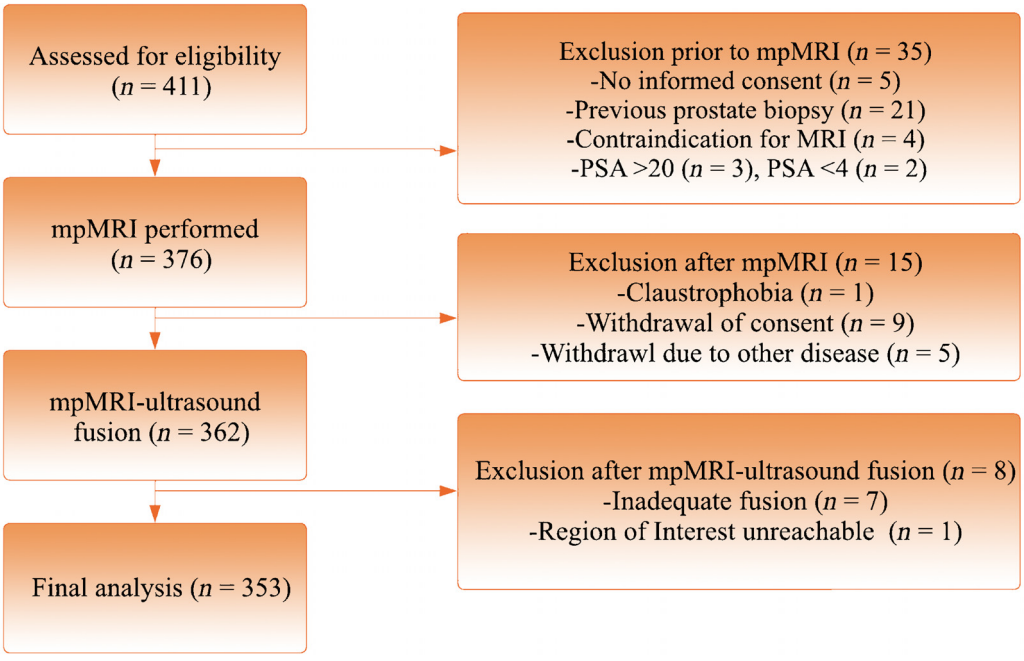

Fig. 1 – Inclusion flow chart. mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.

Table 1 – Patient characteristics and mpMRI results

Age, mean (SD)		66.9 (6.39)
PSA (ng/ml), median (range)		6.7 (0.5–19.5)
Volume on TRUS (ml), median (range)		46 (16–225)
PSA density, median (range)		0.14 (0.01–1.5)
DRE findings, *n* (%)	Normal	194 (55.0)
	Abnormal	159 (45.0)
Highest PI-RADS [a] score on mpMRI, *n* (%)	≤2	90 (25.5)
	3	67 (19.0)
	4	132 (37.4)
	5	64 (18.1)
Total suspicious lesions (*n*)		351
Suspicious lesions per patient, median (range)		1 (1–3)

DRE = digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = Prostate-specific antigen, SD = standard deviation; TRUS = transrectal ultrasound scan.
[a] Based on PI-RADS criteria, version 2.

Table 2 – Detection of prostate cancer in all patients by both biopsy methods combined, systematic biopsies only, and MRI-ultrasound fusion biopsies only.

	Systematic biopsies + MRI-TBx (*n* = 353)	Systematic biopsies (*n* = 353)	MRI-TBx (*n* = 263)
No PCa detected	157 (44.5%)	173 (50.1%)	136 (51.7%)
Non-csPCa	64 (18.1%)	62 (17.6 %)	23 (8.7%)
csPCa	132 (37.4%)	118 (33.4%)	104 (39.5%)

csPCa = clinically insignificant prostate cancer; Gleason ≥3 + 4 (ISUP ≥2); ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; MRI-TBx = magnetic resonance imaging–targeted biopsies; non-csPCa = clinically insignificant prostate cancer, Gleason 3 + 3 (ISUP 1); PCa = prostate cancer.

because of suspicious mpMRI (PI-RADS ≥3). Systematic biopsies were performed in all patients, irrespective of mpMRI results. The detection of PCa in all patients in relation to the mpMRI PI-RADS score is shown in Figure 2. The detection rate for csPCa in the group with suspicious mpMRI was 104/263 (39.5%) for MRI-TBx and 113/263 (42.9%) for systematic biopsies (Fig. 3). Overall, systematic biopsies diagnosed 180/353 (51%) cases of PCa, among which 118 (65.6%) harbored csPCa. By contrast, MRI-TBx diagnosed 127/263 (48.3%) cases of PCa, among which 104 (81.9%) harbored csPCa. In patients with nonsuspicious mpMRI, five cases (6%) of csPCa were found by systematic biopsies (Fig. 2). Figure 3 shows the agreement analysis between systematic biopsies and MRI-TBx. The added values, defined as the additional percentages of patients with csPCa detected by adding one biopsy technique, were 23/263 (8.7%) for the systematic biopsies and 14/263 (5.3%) for MRI-TBx (Fig. 3).

The sensitivity and specificity of combining mpMRI and MRI-TBx for csPCa were 76.3% (95% CI, 67.4–83.4) and 94% (95% CI, 90.0–97.0), respectively; this corresponded to 61.7% (95% CI, 54.1–68.7) sensitivity and 90.8% (95% CI, 85.2–94.5) specificity for all PCa. The negative and positive predictive values for mpMRI and MRI-TBx combined relative to systematic biopsies were 88.8% (95% CI, 84.0–92.0) and 86.5% (95% CI, 78.1–92.2), respectively. Among patients with suspicious mpMRI, no PCa was found in 91 cases (PI-RADS 3, 4, and 5 in 43, 40, and eight cases, respectively).

4. Discussion

In our prospective cohort of biopsy-naïve patients, MRI-TBx detected 39.5% cases of csPCa in case of suspicious mpMRI. Performing concurrent systematic biopsies resulted in an added value of 8.7% of csPCa cases. Abstaining from biopsies in case of nonsuspicious mpMRI would have led to missing five (6%) csPCa cases. The sensitivity and specificity of combining mpMRI and MRI-TBx for csPCa were 76.3% and 94%, respectively.

We believe that this prospective cohort study contributes to the body of evidence that exists on mpMRI and MRI-TBx in biopsy-naïve patients. Of note, this study benefited from comparing both diagnostic approaches in the same patient, at the same visit, and by the same urologist who was blinded to the mpMRI results. It differs from other studies by selecting only biopsy-naïve patients [6], perform-

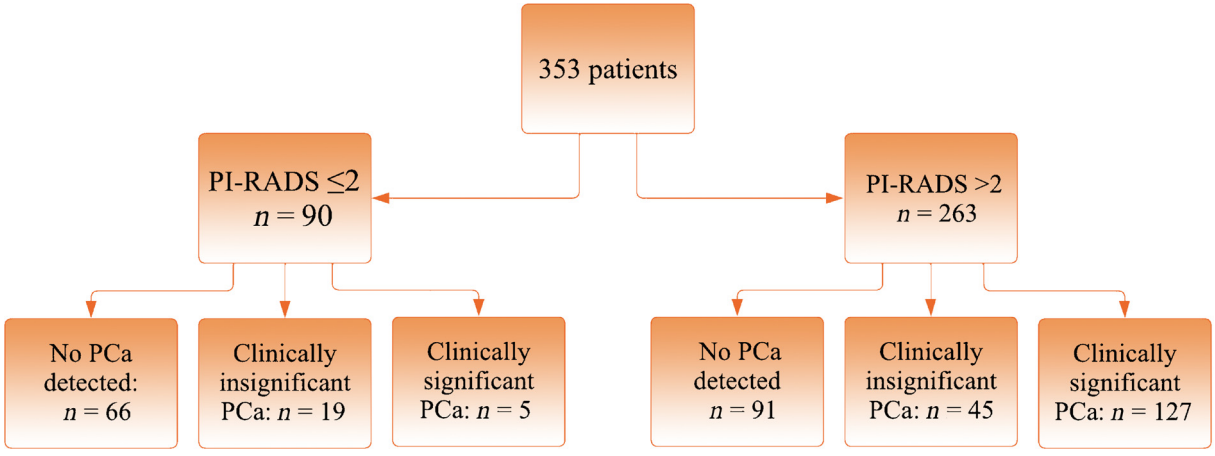

Fig. 2 – Detection of prostate cancer in all patients by mpMRI result. mpMRI = multiparametric magnetic resonance imaging; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System.

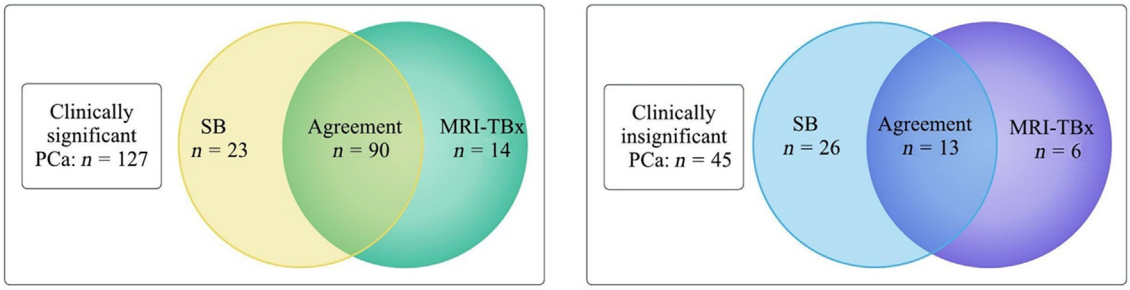

Fig. 3 – Agreement in the detection of PCa between SB and MRI-TBx and their added cases respectively in patients with suspicious mpMRI (PI-RADS >2). MRI-TBx = magnetic resonance imaging-ultrasound fusion biopsies; PCa = prostate cancer; SB = systematic biopsies.

ing both systematic and MRI-TBx or sham biopsies in all patients irrespective of mpMRI results [2,5], and performing MRI-TBx in a uniform [3] and widely available method using the mpMRI-ultrasound fusion technique instead of an expensive time-consuming technique such as the in-bore approach [4]. However, this study has several limitations that are worth elaborating on. In the present study, MRI-TBx detected csPCa in 39.5% of cases with an added value of 8.7% for systematic biopsies, which is higher than that in other studies showing 5.5–7.5% added values [3,6,12]. One explanation could be that no cognitive fusion was applied since operators were blinded to mpMRI results before the start of the procedure. This factor could contribute to an underestimation of the detection rate for csPCa in this cohort. In daily practice, it is anticipated that clinicians will combine MRI-TBx with cognitive fusion using their knowledge of mpMRI images to improve the detection of csPCa.

Furthermore, a major limitation of this study was the choice to perform two MRI-TBx directly from the PI-RADS $\geq$3 lesion. At the time of designing this study, the question about the optimal number of targeted cores was not well explored. Nowadays, there is growing evidence that increasing the number of cores per target lesion enhances the yield of csPCa [13]. Furthermore, perilesional targeted biopsies may increase the performance of MRI-TBx. A recent paper by Brisbane et al [14] sheds light on this issue by determining the distance between the MRI lesion and cores containing csPCa. They show that perilesional biopsies, taken from a band of 10 mm outside the MRI lesions, can detect up to 26% more cases of csPCa that are not present within the lesion. In addition to perilesional targeted biopsies, regional systematic biopsies are being investigated [15]. In our cohort, systematic biopsies detected csPCa in 23 cases of negative MRI-TBx (four non-csPCa and 19 no PCa), suggesting MRI-TBx failure. By comparing the side of the lesion on mpMRI with the side of systematic biopsy containing csPCa, we found 16 cases in which the csPCa-positive systematic biopsy side matched the side of the lesion on mpMRI, implying MRI-TBx failure. This suggests room for improvement of MRI-TBx in our cohort by using perilesional targeting and/or an increased number of cores per target lesion.

On the contrary, in our patients with suspicious mpMRI, no PCa was found in 91 cases (25.7%). Other studies also displayed a substantial number of negative biopsies in case of suspicious mpMRI in up to 18–37% of cases [2,4,6]. Although follow-up for these patients is not yet standardized, a recent study found that 4.9% of patients were diagnosed with csPCa in the follow-up [16]. Our cohort is currently in follow-up and will be analyzed for any csPCa development in the future. The positive predictive value of mpMRI depends not only on PI-RADS score, but also on the prevalence of PCa in the studied population. A meta-analysis demonstrated that mpMRI cannot reliably predict the presence of csPCa when it is scored as PI-RADS 3 [17].

Hypothetically, using mpMRI as a triage test and abstaining from systematic biopsy in case of nonsuspicious mpMRI could have led to missing 6% of csPCa cases. These results confirm previously published data and support the practice of abstaining from routine systematic biopsy when mpMRI is not suspicious [4]. Current European Association of Urology guidelines state that systematic biopsies should be omitted only after careful shared decision-making if mpMRI is negative in low-risk patients, with risk stratification being key to deciding when one can omit biopsies [8]. In practice, the 5-yr detection rates for csPCa in men with repeatedly negative mpMRI results are low, and any PCa found during follow-up is usually nonsignificant [12]. Radiologists' experience is known to be crucial in increasing mpMRI reliability, indicating that a standardized mpMRI-assessment training protocol for radiologists could achieve higher agreement on PI-RADS classifications [7]. Further research should focus on techniques, such as quantitative analysis of imaging data using radiomics, to improve accuracy of mpMRI [18,19].

5. Conclusions

In conclusion, based on our data and existing evidence, we propose that in case of nonsuspicious mpMRI, one could abstain from systematic biopsies after careful shared decision-making. In our cohort, systematic biopsies added a substantial number of csPCa cases and thus should not be omitted in case of suspicious mpMRI. The debate on whether or not systematic biopsies in addition to MRI-TBx can be omitted fully remains ongoing. Further prospective data are required to determine the optimal biopsy protocol with perilesional MRI-TBx and/or additional regional systematic biopsies in order to reduce the number of missed

cases of csPCa and also to minimize the odds of detecting insignificant cancer.

***Author contributions*:** Nicolette G. Alkema had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Alkema, Hoogeveen, Cauberg, Witte, Blanker, Boomsma.
Acquisition of data: Alkema, Hoogeveen, van 't Veer-ten Kate, De Boer, Hoogland.
Analysis and interpretation of data: Alkema, Hoogeveen.
Drafting of the manuscript: Alkema, Hoogeveen.
Critical revision of the manuscript for important intellectual content: Cauberg, Witte, Blanker, Boomsma, Steffens.
Statistical analysis: Alkema, Hoogeveen.
Obtaining funding: Boomsma, Steffens.
Administrative, technical, or material support: van 't Veer-ten Kate, De Boer.
Supervision: Cauberg, Witte, Blanker.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.08.005.

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