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Endometrial compaction and ongoing pregnancy in modified natural cycle frozen euploid embryo transfer: a prospective multicentre cohort study with standardized transvaginal ultrasound assessment

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ABSTRACT

STUDY QUESTION: Does endometrial compaction, assessed by transvaginal ultrasound at two measurement time points, predict ongoing pregnancy in patients undergoing single euploid blastocyst transfer in a modified natural cycle frozen embryo transfer (mNC-FET)?

SUMMARY ANSWER: Endometrial compaction of ≥5% between the day of ovulation triggering and the day of embryo transfer was not associated with ongoing pregnancy rate or any secondary reproductive outcome in this prospective multicentre cohort.

WHAT IS KNOWN ALREADY: Endometrial compaction—a reduction in endometrial thickness (EMT) following progesterone-induced secretory transformation—has been proposed as a potential marker of endometrial receptivity in FET cycles. However, existing evidence is conflicting. Retrospective studies have reported positive associations between compaction and ongoing pregnancy in programmed cycles, while prospective data, including the only prior study restricted to euploid single FET, have not confirmed this relationship. Crucially, most studies have used transabdominal ultrasound for the transfer-day measurement, a recognized source of measurement error. No prospective study has examined compaction exclusively in mNC-FET using transvaginal ultrasound at both time points.

STUDY DESIGN, SIZE, DURATION: Prospective multicentre observational cohort study conducted between March 2023 and March 2025 across six assisted reproduction units of Instituto Bernabeu group (Spain). A total of 207 patients who met all inclusion criteria and completed the full protocol were analysed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women aged 18–50 years undergoing mNC-FET with a single euploid blastocyst (confirmed by preimplantation genetic testing for aneuploidy via next-generation sequencing) were included. EMT was measured transvaginally at T1 (day of hCG trigger) and T2 (day of embryo transfer). Compaction was defined as a ≥5% reduction in EMT from T1 to T2. Additional thresholds of ≥10% and ≥15% were evaluated as sensitivity analyses. The primary outcome was ongoing pregnancy, defined as foetal cardiac activity at 10 weeks of gestation. Multivariable logistic regression was performed, adjusting for age, previous live births, previous miscarriages, BMI, and oocyte origin.

MAIN RESULTS AND THE ROLE OF CHANCE: Of 207 patients, 58 (28.0%) met the compaction criterion (≥5%). The compaction group had a significantly greater T1 EMT (9.55 ± 1.54 mm vs 8.39 ± 1.14 mm, $P < 0.001$) and a lower T2 EMT (7.91 ± 1.19 mm vs 9.75 ± 1.55 mm, $P < 0.001$). Ongoing pregnancy rates were 50.0% in the compaction group versus 53.7% in the non-compaction group ($P = 0.633$). This difference was not significant on multivariable analysis (adjusted odds ratio 0.80, 95% CI 0.38–1.67, $P = 0.546$). The null association was

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consistent across all compaction thresholds (≥10%: $P = 0.674$; ≥15%: $P = 0.928$) and across all secondary outcomes, including clinical pregnancy rate (56.9% vs 59.1%, $P = 0.777$), biochemical pregnancy loss (10.8% vs 8.3%, $P = 0.737$), and early pregnancy loss rate (12.1% vs 9.1%, $P = 0.734$). The overall ongoing pregnancy rate was 52.7% (109/207).

LIMITATIONS, REASONS FOR CAUTION: The distribution between groups was asymmetric (28% compaction vs 72% non-compaction), deviating from the balanced allocation anticipated at protocol design, which may reduce statistical power. Although both measurements were transvaginal, a subset of T1 measurements from international patients were performed at external centres and validated remotely by Instituto Bernabeu's physicians. Live birth data were only partially available at the time of analysis; however, ongoing pregnancy at 10 weeks is a validated and widely accepted surrogate for live birth in reproductive medicine trials.

WIDER IMPLICATIONS OF THE FINDINGS: These findings do not support the hypothesis that endometrial compaction is associated with improved reproductive outcomes in mNC-FET with euploid embryos. The consistent null result across multiple thresholds and outcomes, obtained with a fully standardized transvaginal ultrasound methodology, strengthens the current evidence base. Routine assessment of endometrial compaction with the aim of identifying patients with a favourable prognosis does not appear to be clinically justified in this setting; indeed, acting upon compaction status could lead to unnecessary cycle cancellations in patients who would otherwise achieve ongoing pregnancy.

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Introduction

Embryo implantation is a complex and incompletely understood process that requires precise molecular and cellular dialogue between the developing embryo and the receptive endometrial surface (Bergh and Navot, 1992). Transvaginal ultrasound monitoring of the endometrial thickness (EMT) at the end of the oestrogenic phase remains the most widely used clinical tool to assess endometrial adequacy and to identify the implantation window prior to embryo transfer (Craciunas *et al.*, 2019).

Far less is known about endometrial changes after progesterone exposure. Endometrial compaction (EC), defined as a reduction in EMT between the end of the proliferative phase and embryo transfer, has been proposed as a potential marker of appropriate secretory transformation. However, whether this phenomenon reflects enhanced endometrial receptivity or merely an epiphenomenon without biological significance remains uncertain.

Over the past decade, studies evaluating the association between EC and reproductive outcomes have produced conflicting results. While some retrospective studies suggested improved pregnancy outcomes in association with compaction, subsequent prospective studies have failed to confirm these findings consistently. Interpretation of the available evidence is further complicated by important methodological heterogeneity, including the inclusion of both programmed and natural-cycle frozen embryo transfer (FET) protocols, mixed embryo ploidy status, and differences in ultrasound methodology, with several studies relying on transabdominal assessment at embryo transfer rather than the more accurate transvaginal approach (Haas *et al.*, 2019; Riestenberg *et al.*, 2021; Shah *et al.*, 2022; Youngster *et al.*, 2022).

Consequently, the clinical relevance of EC in modified natural-cycle FET remains uncertain. To our knowledge, no prospective study has evaluated this question exclusively in modified natural cycles (mNCs) using transvaginal ultrasound at both measurement time points and restricting the analysis to single euploid blastocyst transfers.

The present study was designed to address these gaps. Our primary aim is to compare ongoing pregnancy rates according to the presence or absence of EC. We only included patients undergoing single euploid blastocyst transfer in a mNC. EC was defined as a reduction in EMT of ≥5% between the day of ovulation trigger and the day of embryo transfer. Both measurements were obtained exclusively by transvaginal ultrasound, thereby eliminating a recognized source of measurement error in previous studies. Secondary outcomes include biochemical pregnancy rate, clinical pregnancy rate, early pregnancy loss, and ectopic pregnancy rate.

Materials and methods

Study design and setting

This was a multicentre prospective observational cohort study conducted across six assisted reproduction units of the Instituto Bernabeu group (Alicante, Madrid, Albacete, Cartagena, Elche, and Mallorca, all in Spain) between March 2023 and March 2025. The study protocol has been previously published (De la Torre Perez *et al.*, 2023) and was approved by the Ethics Committee of the Alicante General University Hospital (code 22/053Tut). The study was prospectively registered in ClinicalTrials.gov (NCT05960370). All participants provided written informed consent prior to inclusion.

Participants

Eligible patients were women aged 18–50 years with primary or secondary infertility undergoing endometrial preparation in a mNC for single frozen euploid blastocyst transfer. All embryos had previously undergone trophectoderm biopsy for preimplantation genetic testing for aneuploidy via next-generation sequencing, followed by vitrification at the blastocyst stage. Both autologous and donor oocyte cycles were eligible.

Exclusion criteria were: uterine or endometrial pathology (myomatosis with more than three fibroids exceeding 3 cm, adenomyosis, and Asherman syndrome); anatomical conditions precluding accurate transvaginal ultrasound assessment (retroverted or severely tilted uterus); history of recurrent implantation failure (three or more good-quality blastocyst transfers without implantation in patients under 35 years using autologous oocytes or in donor oocyte cycles); history of recurrent early pregnancy loss (two or more spontaneous losses before 10 weeks of gestational age); and suboptimal endometrial response, defined as an EMT below 7 mm on the day of ovulation triggering.

A total of 207 patients who met all inclusion criteria and completed the full study protocol were analysed. A larger number of patients initiated the study cycle but were not included in the final cohort, primarily due to the absence of a documented EMT measurement on the day of embryo transfer, which was required for the definition of the primary exposure variable (Supplementary Fig. S1).

mNC protocol

Women with regular menstrual cycles (28 ± 7 days) underwent transvaginal ultrasound monitoring from cycle days 7–10, adjusted according to individual cycle length, to assess follicular growth and endometrial development. Monitoring was repeated every 2 days as clinically indicated. No routine hormonal assessment was performed before ovulation triggering. Ovulation was triggered with 6500 IU of recombinant hCG (Ovitrelle®; NV Organon) only when both a leading follicle measuring 17–20 mm and an EMT ≥7 mm were present. If the leading follicle reached 17–20 mm but EMT remained <7 mm, ultrasound was repeated after 48 h before deciding on trigger administration. Cycles with sonographic evidence suggestive of spontaneous ovulation before both criteria were fulfilled were excluded from the study. Vaginal progesterone supplementation (400 mg, Cyclogest®; Gedeon Richter) was initiated at bedtime 2 days after hCG administration and continued until 7 weeks of gestation if pregnancy was achieved. Single euploid blastocyst transfer was performed 7 days after the hCG trigger.

Ultrasound measurements

Two transvaginal ultrasound measurements of EMT were obtained for each participant. The first measurement (T1) was performed within 1 day of ovulation triggering and recorded the maximum EMT in a longitudinal uterine view. The second measurement (T2) was obtained on the day of embryo transfer, immediately prior to the procedure, by the attending gynaecologist performing the transfer.

For patients receiving monitoring at external centres—a circumstance arising from the international referral profile of our institution, with patients predominantly from across Europe—the T1 measurement was accepted provided that the attending physician at the external centre supplied both a standardized measurement report and ultrasound images, which were subsequently reviewed and validated by an Instituto Bernabeu gynaecologist before authorizing the trigger injection. Cases with inadequate image quality, unclear anatomical landmarks, or discrepant measurements that could not be confidently validated were excluded from the study. All T2 measurements were performed exclusively at Instituto Bernabeu facilities. A total of 26 gynaecologists participated in the T1 and T2 ultrasound assessments. EMT measurements followed established transvaginal ultrasound methodology routinely used in reproductive medicine. Before study initiation, the principal investigator conducted a study initiation meeting in which the ultrasound protocol and EMT measurement methodology were standardized across participating clinicians. For T1 examinations performed outside Instituto Bernabeu, external sonographers were provided with a standardized ultrasound reporting template to ensure homogeneous documentation of the required measurements.

EC was defined as a reduction in EMT of ≥5% between T1 and T2, calculated as $([T1 - T2]/T1 \times 100)$. Patients were allocated to the compaction group (n = 58) or the non-compaction group (n = 149) on the basis of this criterion.

Outcome measures

The primary outcome was ongoing pregnancy rate, defined as the presence of foetal cardiac activity on transvaginal ultrasound at 10 weeks of gestational age. Secondary outcomes were biochemical pregnancy rate (positive serum β-hCG at 9 days post-transfer), biochemical pregnancy loss (pregnancy detected by serum β-hCG that declined to negative without ultrasonographic evidence of a clinical pregnancy), clinical pregnancy rate (visualization of one or more gestational sacs or definitive clinical signs of pregnancy between 6 and 9 weeks), early pregnancy loss (spontaneous demise before 10 weeks of gestational age), and ectopic pregnancy rate. All outcome definitions followed the terminology proposed by the international glossary on infertility and fertility care (Zegers-Hochschild *et al.*, 2026) and the ESHRE early pregnancy special interest group consensus (Kolte *et al.*, 2015).

Statistical analysis

The sample size calculation was performed prospectively during protocol development (De la Torre Perez *et al.*, 2023), based on the best available evidence at that time. Specifically, we assumed an absolute difference of 20 percentage points between groups (50% vs 70%), derived from the effect sizes reported by Haas *et al.* (2019) and Zilberberg *et al.* (2020). Using a two-sided significance level of 0.05 and a statistical power of 80%, 93 patients per group were required. After allowing for a 15% attrition rate, the target sample size was 206 patients. Although the original sample size calculation was informed by live birth estimates available in the literature, the study protocol prespecified ongoing pregnancy as the primary outcome.

Qualitative variables are expressed as frequencies and percentages; quantitative variables as means with SDs or medians with interquartile ranges, according to distributional normality, assessed with the Kolmogorov–Smirnov test. Between-group comparisons of categorical variables were performed using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Student's *t*-test for normally distributed data or the Wilcoxon rank-sum test for non-parametric distributions. The association between compaction as a continuous variable and endometrial measurements, serum progesterone, and baseline characteristics was assessed using simple linear regression. Multivariable binary logistic regression was performed to evaluate the independent association between EC and ongoing pregnancy, adjusting for the following prespecified covariates: maternal age, BMI, history of prior miscarriages, history of prior live births, and oocyte origin (autologous fresh, autologous vitrified, donated fresh, or donated vitrified). Results are

expressed as odds ratios (OR) with 95% CIs. A *P*-value below 0.05 was considered statistically significant. All analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and open-source software R (v.4.6.0).

Results

Study population and baseline characteristics

Between March 2023 and March 2025, 207 patients met all inclusion criteria and completed the full study protocol across the six centres. A total of 84/207 (40.6%) patients underwent the baseline (T1) ultrasound examination outside Instituto Bernabeu before referral for embryo transfer (59 in the non-compaction group and 25 in the compaction group). Baseline demographic and cycle characteristics are shown in Table 1. The mean age was 39.1 ± 3.0 years, and the mean BMI was 23.0 ± 3.7 kg/m^2. The majority of patients (72.2%) had no relevant medical history; hypothyroidism was the most frequent comorbidity (16.1%). The predominant cause of infertility was ovarian factor (predominantly diminished ovarian reserve) (47.3%), followed by mixed cause (25.6%) and unexplained infertility (17.4%). Most cycles used autologous oocytes (83%), predominantly from fresh retrieval (73.9%). Using the pre-specified threshold of ≥5% reduction, 58 patients (28.0%) were classified as the compaction group and 149 (72.0%) as the non-compaction group. No significant differences were observed between the compaction and non-compaction groups with respect to baseline demographic, clinical, or reproductive characteristics, including age, BMI, medical history, oocyte origin, and infertility diagnosis (all $P > 0.05$; Table 1). Serum progesterone on the day of embryo transfer was available for 196 patients and did not differ between women who did and did not achieve an ongoing pregnancy (25.95 [IQR 20.60–32.10] vs 26.45 [IQR 22.10–30.90] ng/ml, $P = 0.8$). ROC analysis showed no predictive value (AUC 0.505, 95% CI 0.424–0.587).

Endometrial measurements and compaction

Mean EMT at T1 (day of trigger) was 8.72 ± 1.36 mm for the overall cohort and was significantly greater in the compaction group than in the non-compaction group (9.55 ± 1.54 mm vs 8.39 ± 1.14 mm, $P < 0.001$). Mean EMT at T2 (day of transfer) showed the inverse pattern, being significantly lower in the compaction group (7.91 ± 1.19 mm vs 9.75 ± 1.55 mm, $P < 0.001$) (Table 2). The mean percentage change in EMT across the cohort was 7.59 ± 22.11%.

Linear regression confirmed that T1 EMT was inversely associated with the degree of compaction (β = −7.87, 95% CI −9.82 to −5.92, $P < 0.001$; R^2 = 0.236), while T2 EMT showed a positive association (β = 9.15, 95% CI 7.84–10.46, $P < 0.001$; R^2 = 0.480). Serum progesterone on the day of transfer was not associated with the degree of compaction ($P = 0.737$) (Supplementary Figs S2, S3, and S4).

Primary outcome: ongoing pregnancy rate

The overall ongoing pregnancy rate was 52.7% (109/207 patients). No significant difference in ongoing pregnancy rate was observed between the non-compaction and compaction groups (53.7% vs 50.0%, $P = 0.633$; Table 2). This finding was consistent across all pre-specified

Table 1. Baseline characteristics of the study population according to endometrial compaction status.

Characteristic	Overall (N = 207)[a]	No-compaction (N = 149)[a]	Compaction (N = 58)[a]	*P*-value[c]
Age, years	39.12 (3.02)	39.28 (2.94)	38.69 (3.20)	0.141
BMI, kg/m^2 (n = 166)[b]	23.04 (3.67)	22.99 (3.65)	23.19 (3.75)	0.690
Clinical history (n = 205)[b]	—	—	—	0.427
Cancer	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Abdominopelvic surgery	2 (1.0%)	0 (0.0%)	2 (3.5%)	
Dyslipidaemia	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Endometriosis	5 (2.4%)	5 (3.4%)	0 (0.0%)	
Arterial hypertension	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Hypothyroidism	33 (16.1%)	23 (15.5%)	10 (17.5%)	
Hypothyroidism + endometriosis	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Hypothyroidism + autoimmune disease	1 (0.5%)	1 (0.7%)	0 (0.0%)	
No pathology	148 (72.2%)	108 (73.0%)	40 (70.2%)	
Other	3 (1.5%)	2 (1.4%)	1 (1.8%)	
Autoimmune disease	9 (4.4%)	5 (3.4%)	4 (7.0%)	
Infertility characteristics				
Infertility cause	—	—	—	0.060
Unexplained	36 (17.4%)	22 (14.8%)	14 (24.1%)	
Mixed	53 (25.6%)	44 (29.5%)	9 (15.5%)	
Genetic factor	1 (0.5%)	1 (0.7%)	0 (0.0%)	
Male factor	15 (7.2%)	11 (7.4%)	4 (6.9%)	
Ovarian factor	98 (47.3%)	70 (47.0%)	28 (48.3%)	
Tubal factor	4 (1.9%)	1 (0.7%)	3 (5.2%)	
Oocyte source				
Oocyte origin	—	—	—	0.655
Frozen donor	18 (8.7%)	11 (7.4%)	7 (12.1%)	
Fresh donor	17 (8.2%)	12 (8.1%)	5 (8.6%)	
Frozen autologous	19 (9.2%)	13 (8.7%)	6 (10.3%)	
Fresh autologous	153 (73.9%)	113 (75.8%)	40 (69.0%)	

[a] Data are presented as mean (SD) or number (percentage). Percentages are based on available observations.
[b] BMI was available for 166 patients. Clinical history was available for 205 patients (148 without compaction and 57 with compaction).
[c] *P*-values were obtained using the Wilcoxon rank-sum test or Fisher's exact test, as reported in the statistical analysis.

Table 2. Endometrial characteristics and reproductive outcomes according to embryo compaction status.

Characteristic	Overall	No-compaction	Compaction	*P*-value[b]
Endometrial thickness within one day of ovulation triggering (mm)[a]	8.72 (1.36)	8.39 (1.14)	9.55 (1.54)	<0.001
Endometrial thickness on the day of embryo transfer (mm)[a]	9.23 (1.67)	9.75 (1.55)	7.91 (1.19)	<0.001
Ongoing pregnancy[a]				0.633
No	98/207 (47.3%)	69/149 (46.3%)	29/58 (50.0%)	
Yes	109/207 (52.7%)	80/149 (53.7%)	29/58 (50.0%)	

[a] Values are presented as mean (SD) or n/N (%).
[b] *P*-values were calculated using the Wilcoxon rank-sum test, Welch two-sample *t*-test, or Pearson's χ^2 test, as appropriate.
Ongoing pregnancy rates are reported per embryo transfer.

Table 3. Factors associated with ongoing pregnancy: univariable and multivariable logistic regression analyses.

Variable	No-ongoing pregnancy, n (%)	Ongoing pregnancy, n (%)	Univariable OR (95% CI)	Adjusted OR (95% CI)
Endometrial change				
No-compaction	69 (46.3)	80 (53.7)	Reference	Reference
Compaction	29 (50.0)	29 (50.0)	0.86 (0.47–1.59)	0.80 (0.38–1.67)
Age (years)	39.4 (3.2)	38.9 (2.8)	0.94 (0.86–1.03)	0.94 (0.83–1.06)
BMI (kg/m^2)	23.0 (3.5)	23.1 (3.8)	1.01 (0.93–1.10)	1.00 (0.92–1.10)
Previous miscarriages				
No	68 (50.7)	66 (49.3)	Reference	Reference
Yes	30 (41.7)	42 (58.3)	1.44 (0.81–2.59)	1.79 (0.90–3.67)
Previous live birth				
No	88 (50.3)	87 (49.7)	Reference	Reference
Yes	10 (31.2)	22 (68.8)	2.23 (1.02–5.17)	3.99 (1.35–14.25)
Oocyte origin				
Frozen donor oocytes	13 (72.2)	5 (27.8)	Reference	Reference
Fresh donor oocytes	10 (58.8)	7 (41.2)	1.82 (0.45–7.86)	2.49 (0.55–12.56)
Autologous frozen oocytes	10 (52.6)	9 (47.4)	2.34 (0.61–9.78)	3.73 (0.78–20.30)
Autologous fresh oocytes	65 (42.5)	88 (57.5)	3.52 (1.26–11.42)	5.13 (1.54–21.01)

Data are presented as mean (SD) or n (%), as appropriate. Odds ratios (ORs) were estimated using logistic regression. Adjusted ORs were derived from the multivariable model including all variables shown in the table.

compaction thresholds: ≥5% (53.7% vs 50.0%, $P = 0.633$), ≥10% (53.5% vs 50.0%, $P = 0.674$), and ≥15% (52.8% vs 51.9%, $P = 0.928$; Supplementary Table S1).

On multivariable logistic regression adjusting for age, BMI, previous miscarriages, previous live births and oocyte origin, EC was not associated with ongoing pregnancy (adjusted OR 0.80, 95% CI 0.38–1.67, $P = 0.546$; Table 3). In the adjusted model, previous live birth (adjusted OR 3.99, 95% CI 1.35–14.25; $P = 0.019$) and autologous fresh oocytes (adjusted OR 5.13, 95% CI 1.54–21.01; $P = 0.012$) were associated with ongoing pregnancy compared with no previous live birth and frozen donor oocytes, respectively (Supplementary Fig. S5).

Secondary outcomes

The overall biochemical pregnancy rate was 64.3% (133/207), and the clinical pregnancy rate was 58.5% (121/207). Secondary reproductive outcomes stratified by compaction group are presented in Table 4. The biochemical pregnancy loss rate was 9.0% (12/133), and the early pregnancy loss rate was 9.9% (12/121). None of these outcomes differed significantly between the compaction and non-compaction groups (all $P > 0.05$).

At the time of analysis, 41 live births beyond 24 weeks of gestation had been documented, all with neonatal survival. Mean gestational age at delivery was 38.9 ± 1.4 weeks, and mean birthweight was 3303 ± 448 g. Gestational complications were infrequent: gestational diabetes in two cases (5.0%) and gestational hypertension in one case (2.5%).

Discussion

This prospective multicentre cohort study examined the relationship between EC and reproductive outcomes in 207 patients undergoing single euploid blastocyst transfer in a mNC, with both endometrial measurements obtained exclusively by transvaginal ultrasound. Our principal finding is that EC, defined as a reduction in EMT of ≥5% between the day of ovulation triggering and the day of embryo transfer, was not associated with ongoing pregnancy rate, either in the unadjusted analysis or after multivariable adjustment. This null association was consistent across all tested compaction thresholds (≥5%, ≥10%, ≥15%) and across all secondary reproductive outcomes, including clinical pregnancy rate, biochemical pregnancy loss rate, and early pregnancy loss rate.

Our findings align with those of Shah *et al.* (2022), the most methodologically comparable prospective study to date, which reported no association between EC and live birth rate in 186 single euploid FET cycles across programmed and modified natural protocols. Importantly, our study addresses the principal methodological limitation acknowledged by those authors: the use of transabdominal ultrasound for the transfer-day measurement. It is widely accepted that transvaginal assessment provides greater accuracy for endometrial

Table 4. Secondary reproductive outcomes according to embryo compaction status.

Characteristic	Overall	No-compaction	Compaction	*P*-value[b]
Biochemical pregnancy loss rate[a]				0.737
No	121/133 (91.0)	88/96 (91.7)	33/37 (89.2)	
Yes	12/133 (9.0)	8/96 (8.3)	4/37 (10.8)	
Clinical pregnancy rate[a]				0.777
No	86/207 (41.5)	61/149 (40.9)	25/58 (43.1)	
Yes	121/207 (58.5)	88/149 (59.1)	33/58 (56.9)	
Early pregnancy loss rate[a]				0.734
No	109/121 (90.1)	80/88 (90.9)	29/33 (87.9)	
Yes	12/121 (9.9)	8/88 (9.1)	4/33 (12.1)	

[a] Data are presented as n/N (%).
[b] *P*-values were calculated using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test or Pearson's χ^2 test for categorical variables, as appropriate.
Biochemical pregnancy loss was calculated per biochemical pregnancy and miscarriage per clinical pregnancy. Two ectopic pregnancies were included in the clinical pregnancy and early pregnancy loss outcomes, but not in biochemical pregnancy loss.
Clinical pregnancy rates are reported per embryo transfer.

measurement, and mixed-modality designs introduce non-differential measurement error that may obscure true associations or generate spurious ones. By performing both measurements transvaginally, the present study eliminates this source of variability and provides what is, to our knowledge, the first prospective evidence on EC in mNC euploid FET with a fully transvaginal ultrasound methodology.

Our results also concur with two earlier prospective studies in the context of euploid transfers. Riestenberg *et al.* (2021) found no difference in live birth rate according to compaction status in 259 programmed euploid single FET cycles, and Olgan *et al.* (2022) similarly reported no predictive value of compaction in a prospective cohort of vitrified-warmed transfers. More recently, Pan *et al.* (2025), in a retrospective analysis of more than 16 000 hormone replacement FET cycles using transvaginal ultrasound for both endometrial measurements, likewise found that EC was not independently associated with improved pregnancy outcomes after multivariable adjustment. In contrast, the retrospective series by Haas *et al.* (2019) and Zilberberg *et al.* (2020) reported higher ongoing pregnancy rates in association with compaction in programmed cycles. The discordance between these retrospective findings and the prospective evidence accumulated since then—including the present study—is consistent with the hypothesis that the positive associations observed in retrospective designs may reflect selection bias or unmeasured confounding rather than a causal relationship between compaction and endometrial receptivity. Although Pan *et al.* (2025) also employed transvaginal ultrasound at both measurement time points, their study was restricted to hormone replacement FET cycles. Our findings therefore extend the available evidence to the distinct clinical setting of modified natural-cycle single euploid blastocyst transfer, in which prospective data have remained scarce.

Studies specifically conducted in natural cycle FET are fewer, and their conclusions have been equally inconsistent. Bu *et al.* (2019) found no correlation between compaction and clinical pregnancy in natural cycles with untested blastocysts, while Youngster *et al.* (2022) reported a positive association between compaction and both clinical and ongoing pregnancy rates in unstimulated natural cycles. The heterogeneity between these studies and the present cohort likely reflects differences in the type of natural cycle (stimulated vs unstimulated vs modified), embryo ploidy status, compaction measurement methodology, and the specific ultrasound route employed—precisely the variables that our design sought to standardize.

In line with previous observations by Haas *et al.* (2019) and Shah *et al.* (2022), we found that EC was strongly influenced by baseline EMT at the time of trigger (T1). Specifically, women with a thicker initial endometrium exhibited a higher degree of relative compaction, as demonstrated by the inverse association between T1 EMT and compaction percentage. This pattern suggests that a substantial component of the observed compaction may be driven by the mathematical dependency on the starting value, rather than exclusively reflecting an independent biological process. Conversely, EMT at the time of transfer (T2) showed a strong positive association with the degree of compaction, highlighting the close interrelationship between compaction and the final endometrial state, a parameter that has been consistently associated with implantation outcomes. Taken together, these findings support the concept that T1 EMT, T2 EMT, and relative change are intrinsically interconnected, and disentangling their independent contributions remains challenging.

Building on these findings, the compaction group in our cohort exhibited a significantly greater baseline EMT at T1 compared with the non-compaction group (9.55 vs 8.39 mm, $P < 0.001$), whereas EMT at the time of transfer (T2) was significantly lower (7.91 vs 9.75 mm, $P < 0.001$). Despite these differences in endometrial dynamics, reproductive outcomes were comparable between groups. This observation is clinically relevant, as it suggests that an endometrium that appears relatively thin at the time of transfer following compaction from a thicker baseline may not be biologically equivalent to a persistently thin endometrium, and therefore should not necessarily be interpreted with the same clinical concern. From a physiological perspective, this interpretation is consistent with the known processes of secretory transformation, in which progesterone-driven stromal decidualization and glandular coiling increase tissue density without a proportional increase in volume. This may result in a reduction in ultrasound-measured thickness that more likely reflects endometrial maturation rather than functional impairment. Taken together with our previous analyses, these data further support the concept that baseline thickness, final thickness, and relative compaction are closely interrelated parameters, and that their interpretation should be contextual rather than isolated. Moreover, transfer-day serum progesterone was not associated with ongoing pregnancy in our cohort, consistent with recent evidence suggesting that, unlike in artificial FET cycles, circulating progesterone at this time point has limited prognostic value in modified natural-cycle FET. Further studies are

warranted to clarify whether other specific hormonal or endometrial dynamics underlie these associations.

Taken together, the available prospective evidence—including the present study—does not support the use of EC as a criterion for cycle cancellation or clinical decision-making in mNC euploid FET. Systematic assessment of compaction at the time of transfer, beyond its role as a research variable, appears unlikely to improve outcomes and carries the risk of unnecessary cycle cancellations, as previously cautioned by Shah *et al.* (2022). Our findings are particularly applicable to the growing population of patients undergoing single euploid blastocyst transfer in natural cycle preparation, a practice that increasingly reflects contemporary clinical trends driven by evidence favouring natural over artificial cycle FET in ovulatory women.

The principal strengths of this study are its prospective multicentre design, the restriction to single euploid blastocyst transfers—which eliminates embryo quality and ploidy as confounders—the exclusive use of transvaginal ultrasound for both measurements, and the homogeneous endometrial preparation protocol across all centres. The multicentre nature and inclusion of both national and international patients enhance the generalizability of the findings.

Several limitations must be acknowledged.

First, the distribution between groups was asymmetric (72% non-compaction vs 28% compaction), reflecting the observed prevalence of EC in mNCs rather than the approximately balanced distribution assumed during study planning. Although this reduced the statistical precision of between-group comparisons, the direction and magnitude of the observed effect did not suggest a clinically meaningful advantage of EC, making it unlikely that the absence of statistical significance can be explained solely by insufficient power.

Second, although both measurements were performed transvaginally, the T1 measurement was performed at external centres for a subset of international patients; standardization was ensured through mandatory image review and validation by an Instituto Bernabeu gynaecologist, but inter-observer variability cannot be entirely excluded for this subgroup.

Third, physicians performing the ultrasound assessment on the day of embryo transfer were not blinded to the baseline endometrial measurement, as the treating physician was responsible for both the clinical management of the cycle and the transfer procedure. Although EMT is an objective measurement obtained according to a standardized protocol, the absence of blinding may have introduced a degree of observer bias.

Fourth, serum progesterone levels on the day of embryo transfer were available in a subset of patients and will be analysed in detail in a separate nested study focused specifically on hormonal determinants. In the present cohort, no meaningful differences in serum progesterone at transfer were observed between the compaction and non-compaction groups, suggesting that systemic progesterone levels at this time point are unlikely to be a major driver of the observed compaction patterns.

Fifth, while ongoing pregnancy at 10 weeks was our primary outcome as pre-specified in the published protocol, live birth data were only partially available at the time of analysis (41 confirmed live births), precluding a definitive assessment of the impact of compaction on this endpoint. This limitation is particularly relevant in centres treating a large proportion of international patients, in whom long-term follow-up until delivery is frequently incomplete after return to their home country. Although full live birth data were not available in this analysis, previous methodological work has demonstrated that the use of ongoing pregnancy instead of live birth does not materially alter prognostic model performance or clinical conclusions, supporting its validity as an outcome measure in studies of assisted reproduction (Braakhekke *et al.*, 2014).

Conclusions

In this prospective cohort of patients undergoing single euploid blastocyst transfer in a mNC, EC assessed by transvaginal ultrasound at both time points was not associated with ongoing pregnancy rate or any secondary reproductive outcome. These findings do not support the routine clinical use of EC as a predictor of implantation success in this setting.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

E.D.l.T.-P.: Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review and editing. J.C.C.-F.: Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review and editing. M.C.C.-M.: Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review and editing. J.A.O.: Statistics and editing. B.L.-B.: Investigation, Writing—original draft, Writing—review and editing. S.O.-G.: Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review and editing. B.M.-R.: Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review and editing. A.B.-G.: Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review and editing.

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Disclosures

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