

Combined analysis of endometrial thickness
and pattern in predicting outcome of in vitro
fertilization and embryo transfer:
a retrospective cohort study

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Background

- Endometrial receptivity is critical to successful pregnancy.
 - Sonography in ART treatment:
 - an accurate evaluation and noninvasive detection
 - endometrial thickness and endometrial pattern regarded as prognostic parameters
 - the changes in endometrial structure during the menstrual cycle under periodic ovarian stimulation

Background

- In an IVF /CSI procedure:
 - Evaluation of endometrium on the day of hCG administration is of great clinical importance.
 - endometrial characteristics VS . pregnancy rate ?!
 - VS . pregnancy outcome ?!

Background

- Weissman et al. reported an ↑ in miscarriage rate when an endometrial thickness of > 14 mm was found on the day of hCG injection.
 - Other data?
- A no triple-line endometrial pattern seems to be a prognostic sign of a less favorable outcome, while a **triple-line pattern appear to be associated with conception.**

Background

- Objective:
 - To evaluate the combined effect of endometrial thickness and pattern on clinical outcome in patients undergoing IVF /CSI-ET.

Methods – Study population

- Cycles of IVF /ICSI conducted between January 2003 and December 2008 at a university-based reproductive center were reviewed retrospectively.
- All fresh IVF or ICSI treatment cycles that used the **long protocol** (midluteal phase GnRH-agonist suppression) as the method of ovarian stimulation
- Regardless of diagnosis, reproductive history, or insemination method

M e t h o d s – S t u d y p o p u l a t i o n

- E x c l u s i o n :
 - C y c l e s u s i n g d o n o r o o c y t e s o r c r y o p r e s e r v e d e m b r y o s
 - a g e > 4 2 y e a r s
 - t h e p r e s e n c e o f k n o w n e n d o m e t r i a l a n o m a l i e s
 - o v a r i a n s t i m u l a t i o n m e t h o d o t h e r t h a n t h e l o n g p r o t o c o l

Methods – IVF /CSI-ET treatment protocol

- The long protocol procedure

- each patient received a single IM injection of the GnRH agonist (1.25 mg ~ 1.875 mg) in the midluteal phase of the cycle prior to the initiation of controlled ovarian hyperstimulation (COH).
- After spontaneous menstruation occurred, a vaginal ultrasound examination and serum estradiol concentration (E₂) measurement were performed.

Methods – IVF /CSI-ET treatment protocol

- When the E2 levels were ≤ 50 pg/mL, and the longest follicle diameter was <10 mm without ovarian cysts, COH was performed.
 - administration of gonadotrophin, including the FSH and/or human menopausal gonadotrophin (hMG)
 - The initial dosage of gonadotrophin ranged from 150 ~ 450 IU, depending on the basal FSH level, antral follicular count (AFC), and maternal age.

Methods – IVF /CSI-ET treatment protocol

- Once 3 or more follicles reached a diameter of ≥ 17 mm, hCG was administered.
- Oocytes were retrieved within 34 to 36 hours and ET was performed 2 to 5 days afterwards.
- All patients were given IM P daily starting on the day of oocyte retrieval.
- Serum b-hCG levels were measured 11-14 days after ET.

Methods – IVF /CSI-ET treatment protocol

- Subsequent ultrasound examinations were performed at a gestational age of 7 weeks.
- **Clinical pregnancy** was defined as identification of a gestational sac 2–3 weeks after embryo transfer.
- **Early miscarriage** was defined as pregnancy ending before 12 weeks of gestation.

Methods – Ultrasound examinations

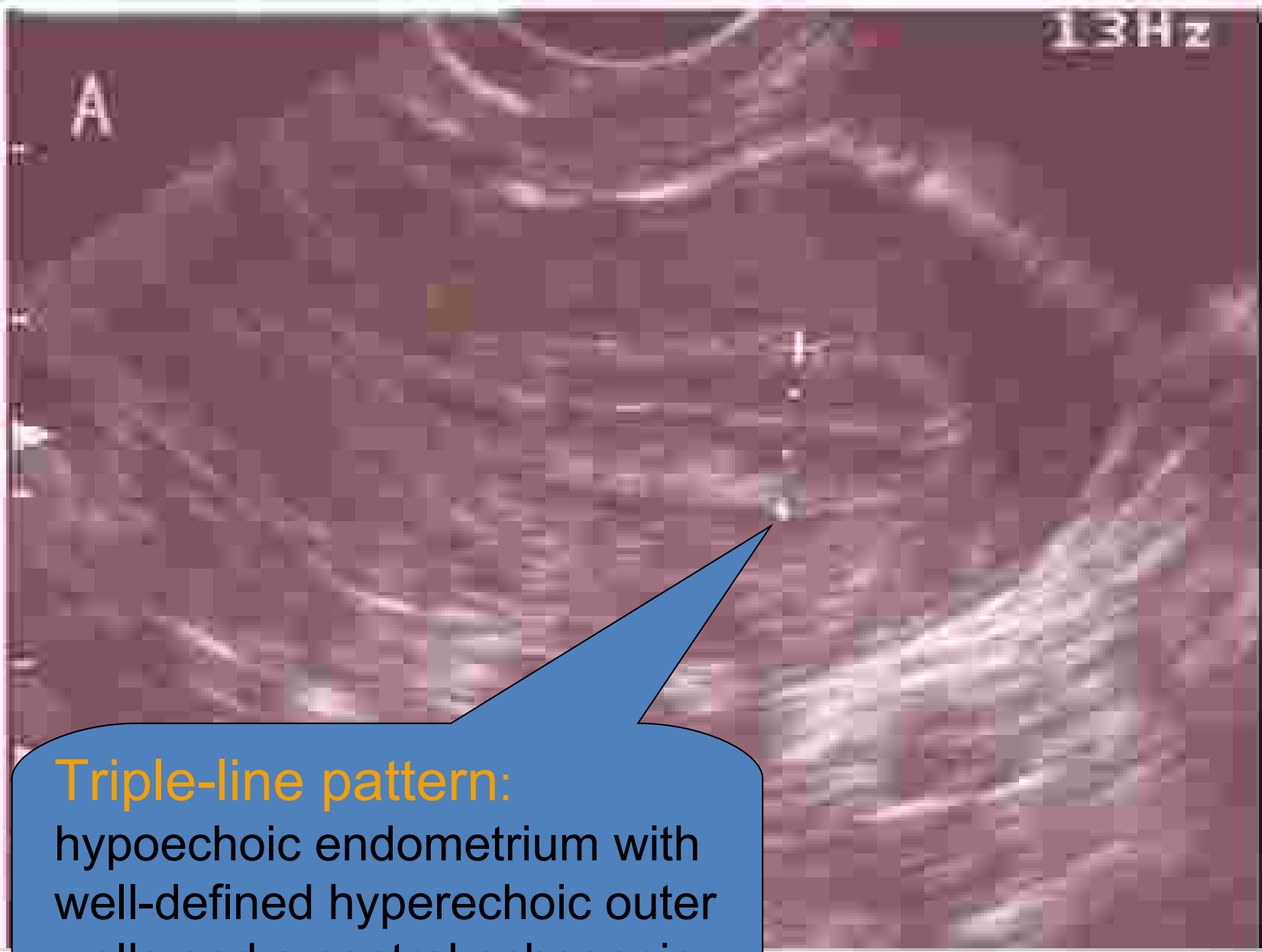
- **Endometrial thickness** was measured on the day of hCG administration.
 - The largest thickness from one interface of the endometrial-myometrial junction to the other was measured.
 - 3 groups:
 - Group 1: ≤ 7 mm
 - Group 2: $> 7 \sim \leq 14$ mm
 - Group 3: > 14 mm

Methods – Ultrasound examinations

- **Endometrial pattern** is defined as the type of relative echogenicity of the endometrium compared with adjacent myometrium.
- 2 types:
 - Pattern A (triple-line)
 - hypoechoic endometrium with well-defined hyperechoic outer walls and a central echogenic line
 - Pattern B (no triple-line)
 - isoechoic or homogeneous hyperechoic endometrium with a non-prominent or absent central echogenic line

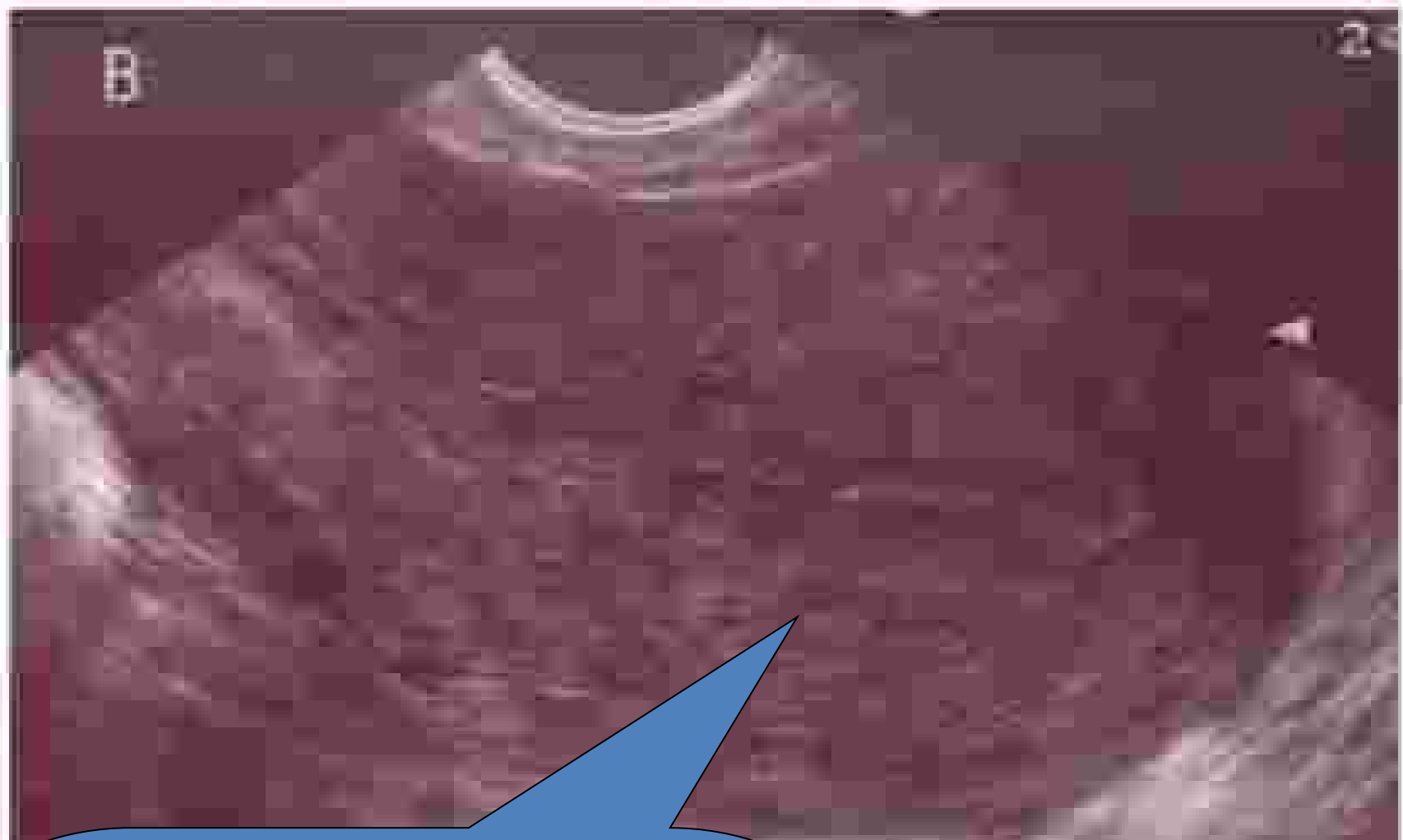
13 Hz

A



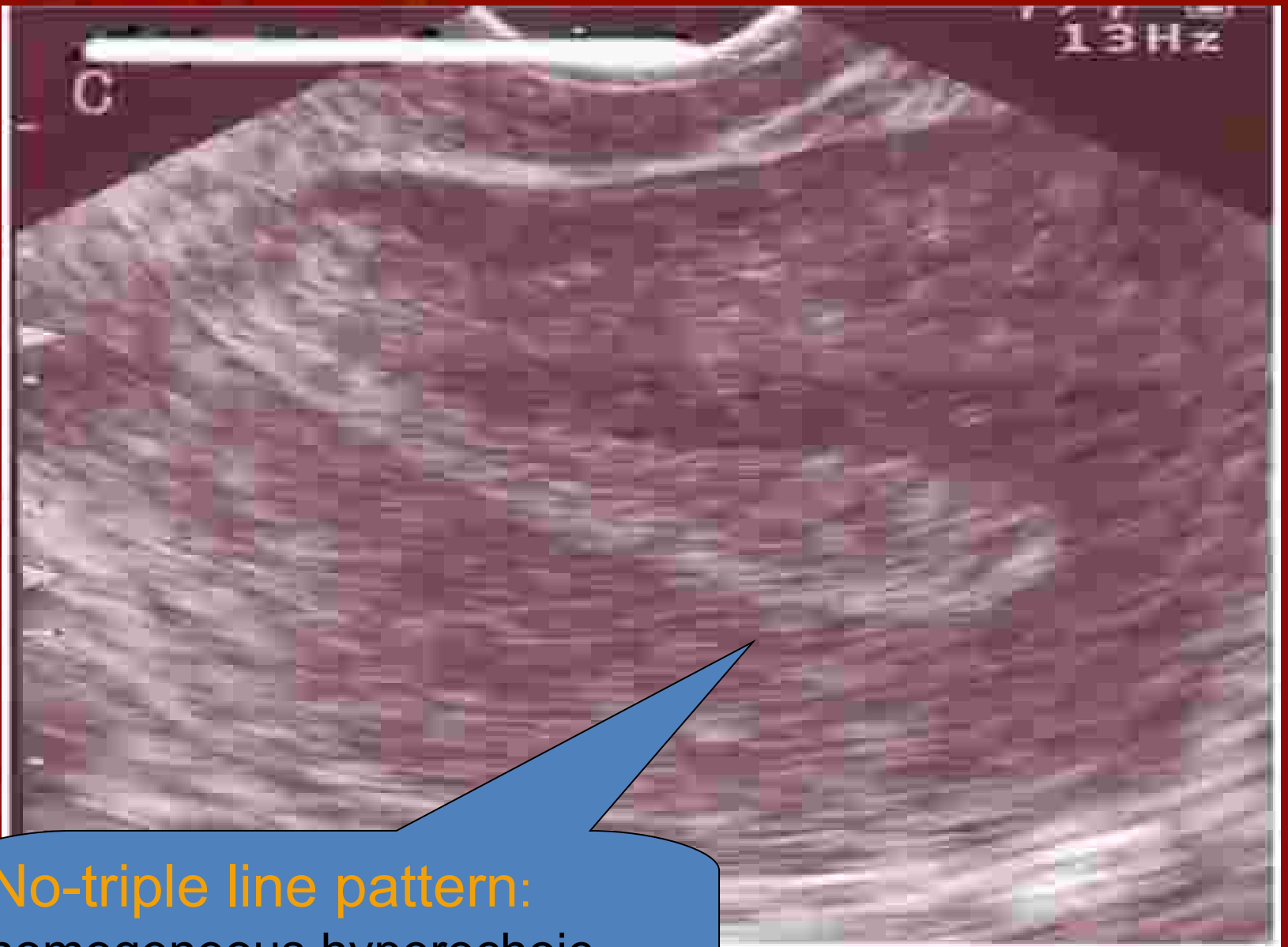
Triple-line pattern:

hypoechoic endometrium with well-defined hyperechoic outer walls and a central echogenic line



No-triple line pattern:
isoechoic endometrium with
poorly defined outer walls and
central echogenic line





No-triple line pattern:
homogeneous hyperechoic
endometrium.

Results – Baseline cycle characteristics

- A total of 2896 IVF/CSI cycles were investigated in this study.
- The overall rates:
 - clinical pregnancy rate: 48.4%
 - early miscarriage rate: 8.4%

Table 1 Baseline cycle characteristics (N = 2896)

Variable	Mean \pm SD ^a	
Maternal age (years)	31.0 \pm 3.9	20 ~ 42
Duration of infertility (years)	5.0 \pm 3.0	
Baseline FSH (IU/L)	7.1 \pm 2.2	
AFC	15.6 \pm 6.8	
Duration of stimulation (days)	11.7 \pm 3.4	
Total dose of gonadotrophin (IU)	2537.3 \pm 1067.2	
Endometrial thickness (mm)	11.8 \pm 2.7	5.2 ~ 26.7
E ₂ on hCG day (pg/mL)	2107.3 \pm 1596.1	
P on hCG day (ng/mL)	1.0 \pm 1.3	
No. of oocyte retrieved	12.7 \pm 6.1	
No. of embryos transferred	2.3 \pm 0.5	
Etiology of infertility		
Tubal factor	55.8%	
Ovulatory dysfunction	1.4%	
Endometriosis	3.2%	
Uterine factor	0.3%	
Male factor	13.4%	
Unknown factor and others	2.2%	
Multiple factors	23.7%	

^aMean \pm SD, unless otherwise indicated

AFC = antral follicular count

P = serum progesterone concentration

E₂ = serum estradiol concentration

Table 2 Binary logistic regression^a (model $R^2 = .028$, $P < .001$)

Independent variables	R^b	p^c
Maternal age	-0.025	0.037
Endometrial thickness	0.060	0.001
AFC	0.027	0.000
Endometrial thickness	0.777	0.378
Baseline FSH level	0.087	0.768
F _u on HCG day	3.000	0.083
Duration of infertility	0.885	0.347

Clinical pregnancy served as dependent variable; Method = forward stepwise (likelihood ratio)

^bPartial coefficients

^cP values, R values were considered statistically non-significant unless $P < 0.05$

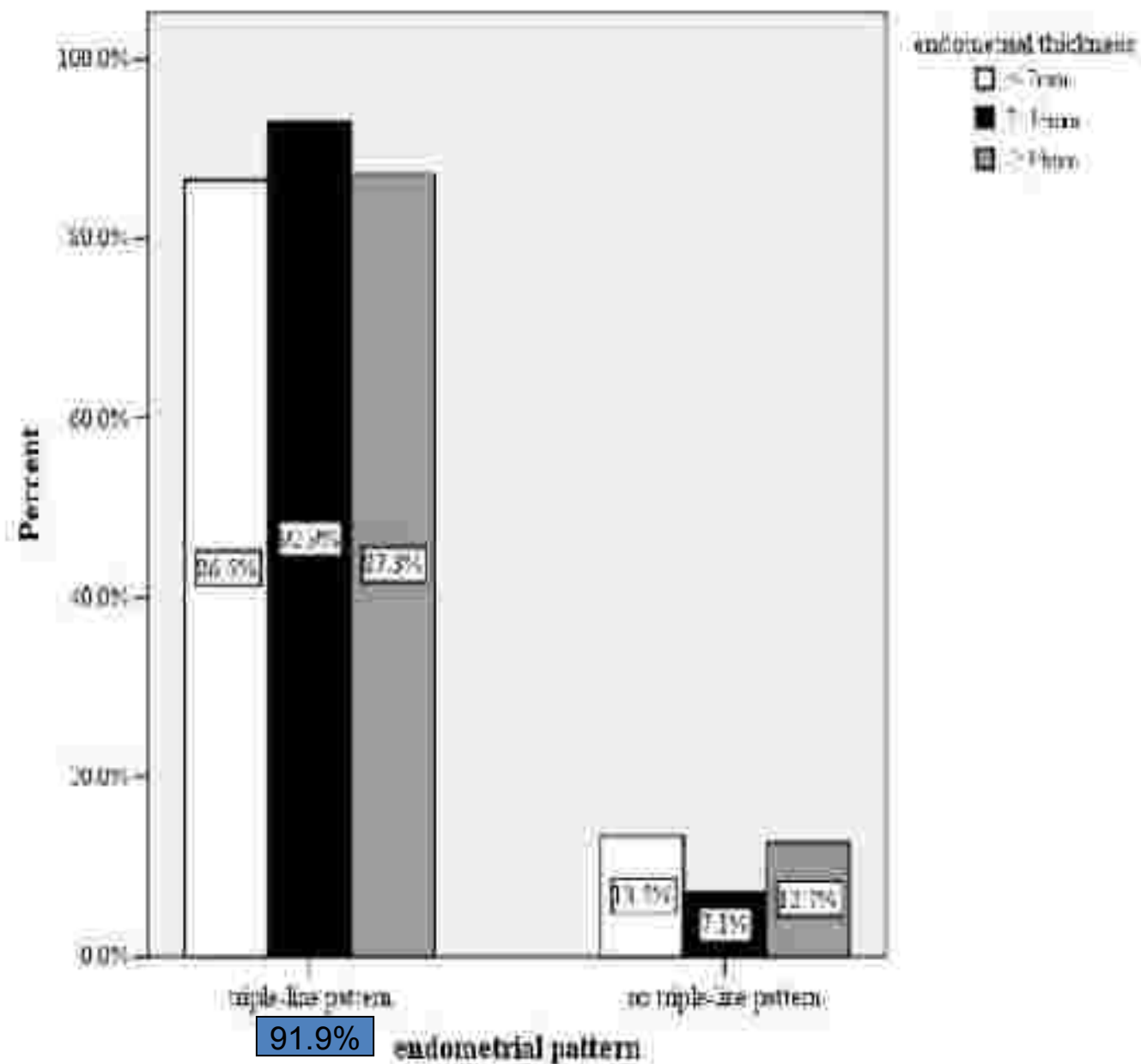


Figure 2 Distribution of endometrial patterns in three endometrial thickness groups. The percentages of endometrial patterns are shown for individual endometrial thickness groups.

Results – Endometrial pattern

- **Pattern A (triple-line)** was detected more frequently in group 2 (EM thickness $> 7 \sim \leq 14$ mm) than in groups 1 and 3 ($P < 0.01$).
- **Progesterone levels on the day of hCG administration** did not differ between the two patterns (0.95 ± 0.82 in pattern A vs 1.04 ± 1.07 in pattern B, $P > 0.05$).

Results – Endometrial pattern

- There was no difference in clinical pregnancy rates between the patterns ($P > 0.05$):
 - pattern A: 48.6%
 - pattern B: 46.2%
- The incidence of miscarriage ($P < 0.05$):
 - pattern B: 15.6% ; significant higher
 - pattern A: 7.9%

Table 3 Clinical outcome by individual endometrial thickness

Endometrial thickness (mm)	Cycles (n)	Clinical pregnancy rate (cycles, %)	Miscarriage rate (n, %)
≤ 6	9	1 (11.1)	0
>6 to ≤ 7	43	11 (25.6)	1 (9.1)
>7 to ≤ 8	142	64 (45.1)	4 (6.3)
>8 to ≤ 9	277	106 (38.3)	13 (12.3)
>9 to ≤ 10	393	191 (48.6)	16 (8.4)
>10 to ≤ 11	424	204 (48.1)	20 (9.8)
>11 to ≤ 12	415	198 (47.5)	14 (7.1)
>12 to ≤ 13	377	185 (49.1)	15 (8.1)
>13 to ≤ 14	320	170 (53.1)	17 (10.0)
>14 to ≤ 15	198	117 (59.1)	9 (7.7)
>15 to ≤ 16	124	57 (46.0)	3 (5.3)
>16 to ≤ 17	71	40 (56.3)	5 (12.5)
>17 to ≥ 26.7	102	59 (57.8)	1 (1.7)

Table 4 Clinical outcome according to thickness grouping and combined grouping of thickness and pattern

Thickness grouping	CPR	Miscarriage rate	CPR by pattern A ²	CPR by pattern B ²	P ³
Group1(n = 22)	23.1%	0.3%	11/25(24.4%)	1/7(14.3%)	NS
Group2(n = 2349)	47.6%	3.9%	1147/7183(69%)	71/166(42.8%)	NS
Group3(n = 495)	55.2%	6.6%	235/432(54.6%)	37/63(58.7%)	NS
P ⁴	< 0.01	NS	< 0.01	< 0.05	*

Endometrial thickness: Group 1: ≤ 7 mm; Group 2: >7 to 14 mm; Group 3: >14 mm

Pattern A = triple-line pattern, hypoechoic endometrium with well-defined hyperechoic outer walls and central echogenic line

Pattern B = nontriple line pattern; isoechogenic or homogeneous hyperechoic endometrium with a poorly defined or absent central echogenic line

CPR = clinical pregnancy rate

¹Percent cycles/total cycles and percentage of clinical pregnancies

²P-values by chi-square test

NS = not significant

Results – Assessing clinical outcome by combined analysis of endometrial thickness and pattern

Table 4 Clinical outcome according to thickness grouping and combined grouping of thickness and pattern

Thickness grouping	CPR	Miscarriage rate	CPR by pattern A ^a	CPR by pattern B ^a	P ^b
Group 1 (n = 32)	23.1%	0.3%	<u>11/65 (24.4%)</u>	<u>17/114 (33%)</u>	NS
Group 2 (n = 2349)	47.6%	1.9%	1147/2183 (49%)	717/1667 (49%)	NS
Group 3 (n = 495)	55.2%	6.6%	235/432 (54.6%)	37/63 (58.7%)	NS
P ^b	< 0.01	NS	< 0.01	< 0.05	*

Endometrial thickness: Group 1: ≤ 7 mm; Group 2: >7 to 14 mm; Group 3: >14 mm

Pattern A = triple-line pattern, hypoechoic endometrium with well-defined hyperechoic outer walls and central echogenic line

Pattern B = nontriple line pattern; isoechogenic or homogeneous hyperechoic endometrium with a poorly defined or absent central echogenic line

CPR = clinical pregnancy rate

^aPresent cycles/total cycles and percentage of clinical pregnancies

^bP-values by Chi-square test

NS = not significant

Discussion

- This study is the largest in terms of sample size to assess the combined effect of endometrial thickness and pattern on clinical outcome.
 - an independent effect of endometrial thickness on pregnancy rate
 - pregnancy rate ↓ markedly as age ↑

Discussion

- The minimum endometrial thickness required for successful pregnancy??
 - no pregnancies occurred when the endometrial thickness was < 7 mm
 - a minimum thickness of 6 mm is acceptable as a prerequisite for implantation
 - a successful pregnancy with an endometrial thickness as little as 4 mm
 - In the present study, the thinnest endometrial lining for successful ongoing pregnancy was 5.3 mm.

Discussion

- An endometrial thickness threshold of 7 mm , below which pregnancy rates ↓ rapidly.
 - The clinical pregnancy rate in group 1 (endometrial thickness ≤ 7 mm) was significantly < groups 2 and 3, being only 23.1% .
 - more attention needs to be given to embryos transferred to such patients

Discussion

- Richter et al. demonstrated a significant \uparrow in the pregnancy rate as endometrial thickness \uparrow , independent of the # and quality of embryos transferred.
 - Confirmed by Ai-Ghamdi et al in a 2464-cycle cohort study.

Table 3 Clinical outcome by individual endometrial thickness

Endometrial thickness (mm)	Cycles (n)	Clinical pregnancy rate (cycles, %)	Miscarriage rate (n, %)
≤6	9	1 (11.1)	0
>6 to ≤7	43	11 (25.6)	1 (2.3)
>7 to ≤8	142	64 (45.1)	4 (2.8)
>8 to ≤9	277	106 (38.3)	13 (4.7)
>9 to ≤10	323	121 (37.5)	16 (4.9)
>10 to ≤11	424	204 (48.1)	20 (4.7)
>11 to ≤12	416	198 (47.6)	14 (3.4)
>12 to ≤13	377	185 (49.1)	15 (3.9)
>13 to ≤14	322	170 (53.1)	17 (5.3)
>14 to ≤15	198	117 (59.1)	9 (4.5)
>15 to ≤16	124	57 (46.0)	3 (2.4)
>16 to ≤17	71	43 (60.6)	5 (7.0)
>17 to ≥20.7	102	59 (57.8)	1 (1.0)

Discussion

High miscarriage rate with (>14 mm)

ward an increase in endometrial thickness increased

- support those of some previous studies in which ↑ endometrial thickness (>14 mm) did not have a detrimental effect on clinical outcome

Discussion

- Consistent with several previous studies, we found that **endometrial echo patterns have no prognostic value for pregnancy.**
- The miscarriage rate in the no triple-line endometrial pattern was significantly higher than in the triple-line pattern.

Discussion

- Several studies have suggested that a premature secretory endometrial pattern is introduced by the advanced P rise
 - has an adverse effect on pregnancy rates
- In the study, \uparrow P concentrations were not found in no-triple line pattern.

Discussion

Table 4 Clinical outcome according to thickness grouping and combined grouping of thickness and pattern

Thickness grouping	CPR	Miscarriage rate	CPR by pattern A ^a	CPR by pattern B ^a	P ^b
Group1 (n = 32)	21.7%	8.3%	71/43(244%)	177(141%)	NS

- Perhaps the coexistence of a **thinner endometrium in association with no-triple line pattern** reflected a diminished endometrial responsiveness to ovarian hormones and poor receptivity of the endometrium, leading to a low clinical pregnancy rate and poor clinical outcome.

Discussion

- Clinical outcomes in pattern B in the other two groups (group 2 and 3) were inconsistent with that in group 1.
 - no differences in clinical pregnancy rates between the two patterns in groups 2 and 3.
 - Check et al, who found that no pregnancies occurred in those patients with homogeneous hyperechoic endometrium.
- The miscarriage rates in groups 2-B was significantly higher than in group 2-A.
 - the adverse effect of pattern B together with a moderate endometrial thickness (7-14 mm) mainly affects the pregnancy outcome, but not the pregnancy rate.

Discussion

- An unexpected finding was a similar miscarriage rate in the two patterns in group 3.
 - Perhaps adequate endometrial thickness (>14 mm) mitigated the detrimental impact (high miscarriage rate) of pattern B endometrial texture.

Discussion

- Limitation:
 - the # of thin endometrial thickness (≤ 7 mm) with no-triple line pattern subjects in the study population was too small to make a definitive statement.

C o n c l u s i o n

- W h e n a t h i n n e r e n d o m e t r i u m (≤ 7 mm) and no triple line endometrial pattern coexist in an IVF/ICSI candidate, **cryopreservation** should be recommended.
- B e c a u s e e n d o m e t r i a l t h i c k n e s s ≤ 7 mm with no-triple line pattern was seen in only 0.3% of cycles in the study, further study is needed to make a definitive conclusion.

Conclusion

- If a thinner endometrium with a good texture (triple-line) is present, other prognostic factors, such as **embryo quality**, should be taken into consideration.
- **Regardless of the endometrial pattern, a thicker endometrium (>14 mm) did not have an adverse effect on the clinical outcome.**

Conclusion

- Combined analysis of endometrial thickness and pattern on the day of hCG administration could be more valuable than the separate analyses.