Does acupuncture improve the prospects for conception?

鍼灸は不妊に効果があるのか？

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Background

- One in seven couples suffer from infertility and many will seek help in the form of assisted reproductive technology (ART).
- The use of acupuncture in the improvement of conception is still controversial.
- Cochrane Report in 2013 showed that use of acupuncture in participants undergoing assisted conception treatment around the time of embryo transfer or at egg collection in terms of improving the live birth rate, ongoing or clinical pregnancy rate showed no evidence of benefit.
- These controversial results have led The British Fertlilty Society to change its guidelines on acupuncture following an announcement that it had found no evidence that having acupuncture or Chinese herbal medicine treatment around the time of assisted conception increases the likelihood of subsequent pregnancy.

Objective

- To extract problems inherent in 2013 Cochrane Report by analyzing the design of the study, patient background, methodology and differences in the results of the acupuncture intervention.

Study Design and Setting

- Twenty randomized controlled trials were included of which four of the trial reports were abstracts. Nine studies were excluded.
- 14 studies are done around ET.
  - It has been shown that the receptivity of the endometrium and the uterine contraction frequency at the time of ET are critical for embryo implantation.
- 6 studies are done around Oocyte retrieval
  - Of which one study was done continuously

Study Characteristics

Acupuncture Method Timing	20 RCT Studies
Before After Embryo Transfer	14 (3632 women)
Before Transfer: Neiguan, Diji, Taixi etc After Transfer: Zusanli, Sanyingjiao, Xuehai, Hegu	
Oocyte Retrieval	5 (876 women)
LFEA: 30 min before retrieval on Hegu, Waiguan, Guilai, Zusanli, Sanyingjia	
Continuous Treatment	1 (44 women)
EA 4 times, twice a week on Taichong, Sanyinjiao, Shuidao, Zicong, Qihai,Guanyuan	

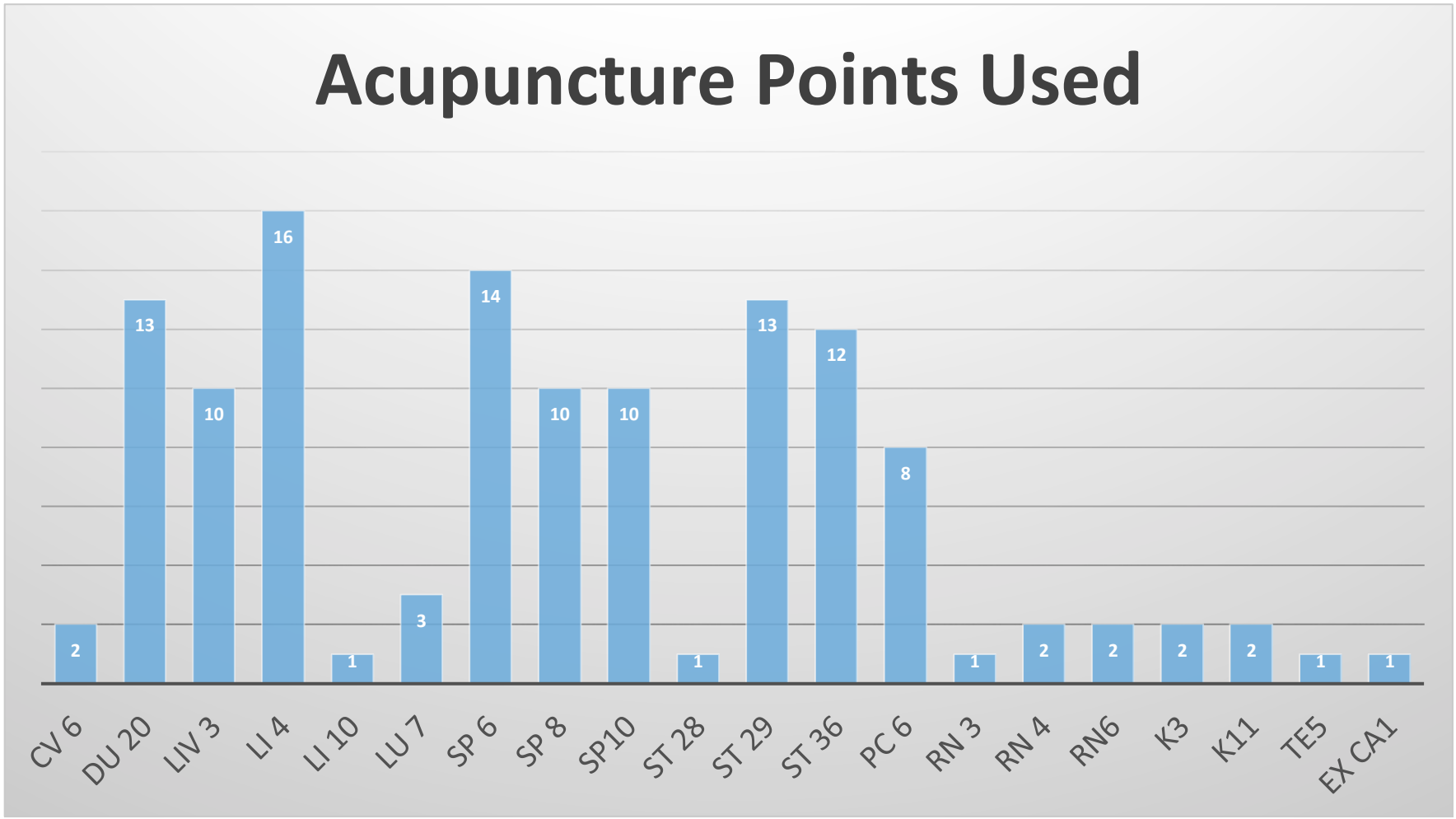
At or around the time of Embryo Transfer

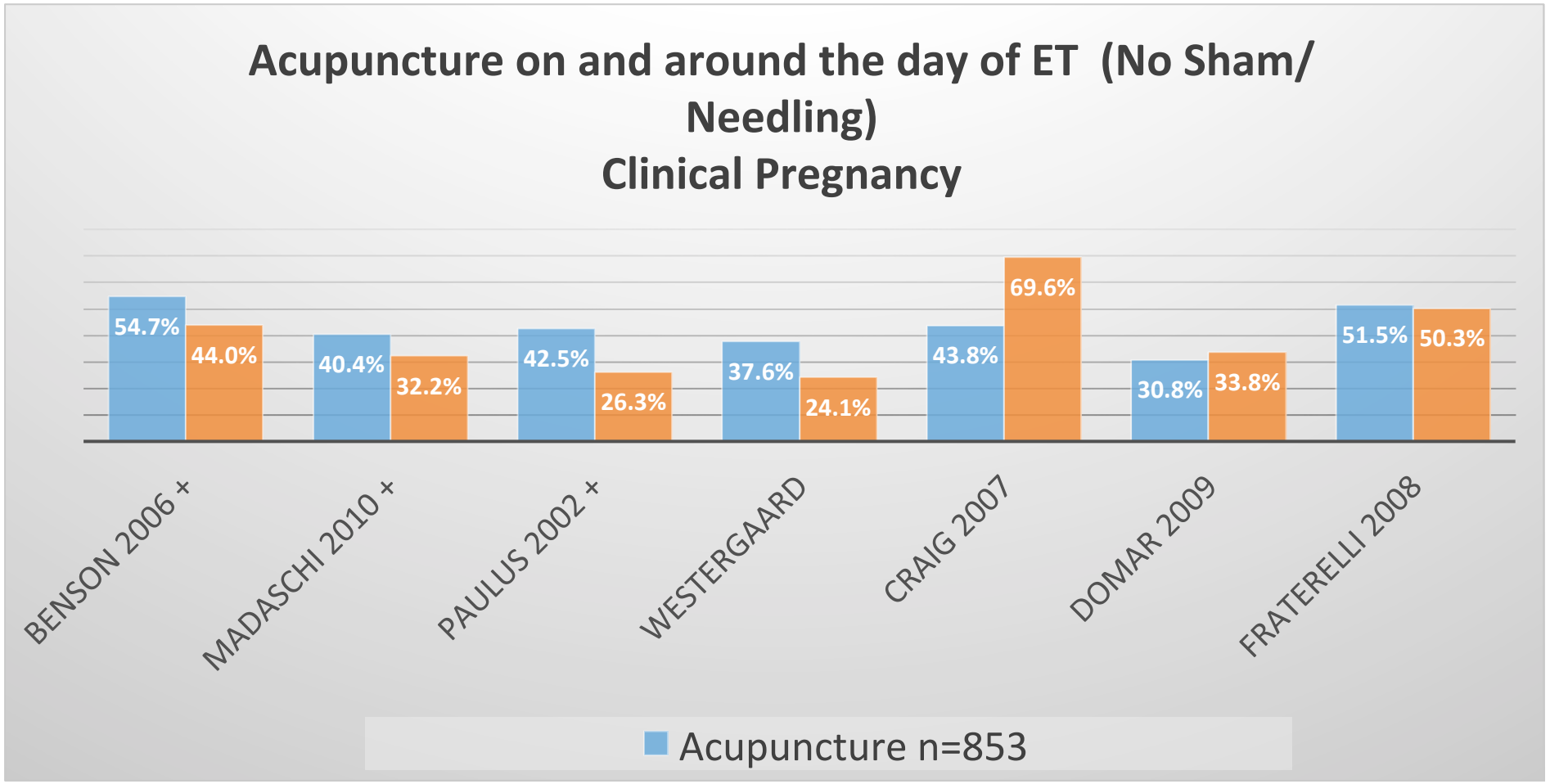
Author/Publication Year	Country	Method	Timing of Intervention	Jadad Score	Result						
					Clinical Pregnancy	Biochemical Pregnancy	Ongoing Pregnancy	Live Birth Rate	Implantation Rate	Miscarriage Rate	others
Paulus/2002	Germany	Acupucture +Ear	BAET Before,After Embryo Transfer	3	○	N/A	N/A	N/A	N/A	N/A	no difference in pulsatility index
Smith/2006	Austrailia	Acupucture +Ear	D9＋BAET	3	×	N/A	×	N/A	N/A	N/A	N/A
Dieterle/2006	Germany	Acupucture +Ear	PT30min＋PT3	2	○	○	○	N/A	○	×	N/A
Westergaard/2006	Denmark	Acupuncture	BAET＋PT2	1	○	N/A	×	N/A	N/A	×	N/A
Domar/2009	US		BAET	4	×	N/A	N/A	N/A	N/A	N/A	reduced stress
So/2009	Hong Kong			5	×	N/A	×	×	×	×	reduction in endometrial vascularity, reduced cortisol and anxiety
Madaschi/2010	Brasil			2	×	N/A	×	×	×	N/A	N/A
Andersen/2010	Denmark			5	×	N/A	N/A	×	×	×	N/A
So/2010	Hong Kong			5	X	N/A	x	x	X	N/A	N/A
May/2011	US			5	×	×	N/A	N/A	N/A	N/A	N/A

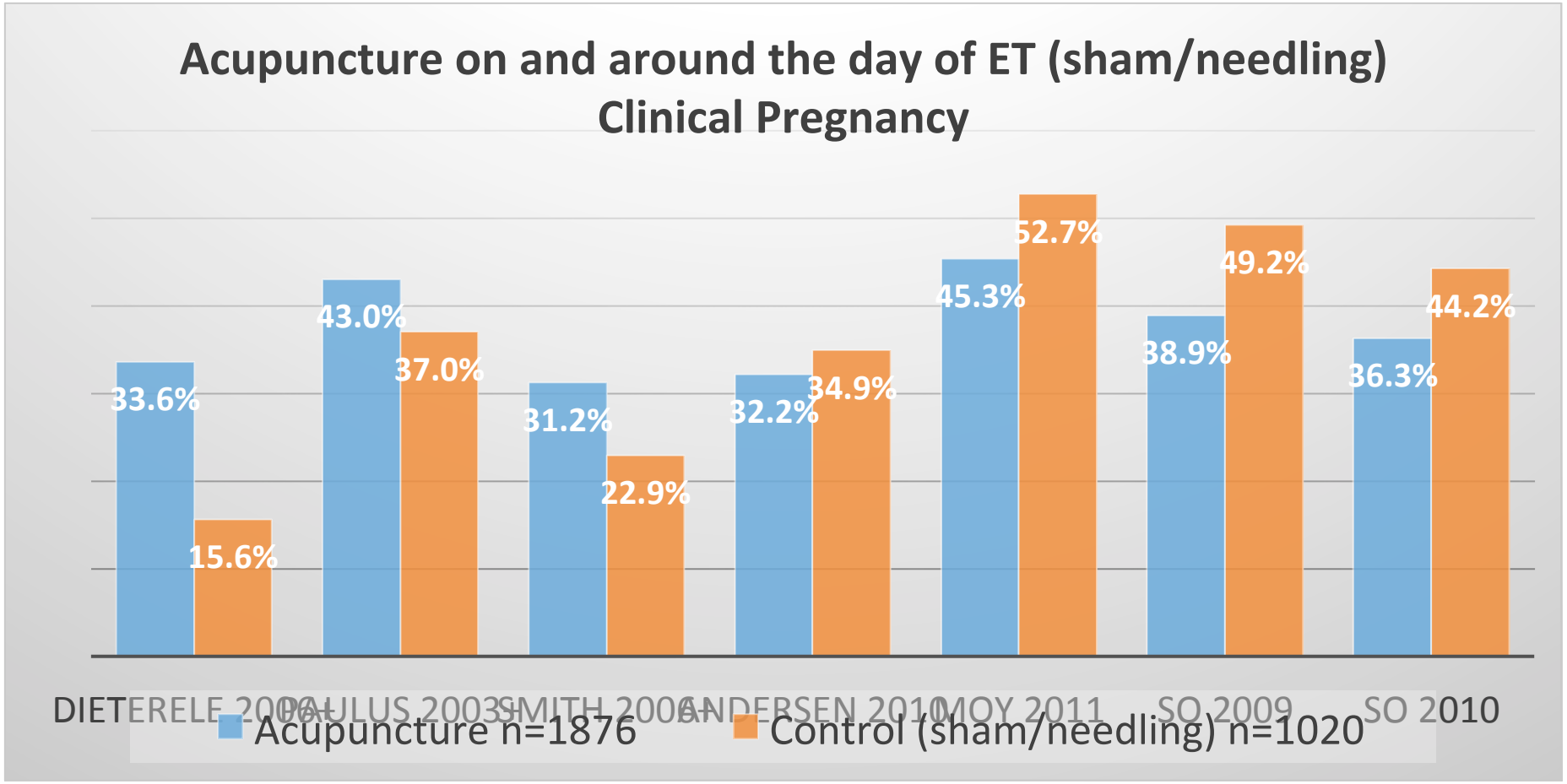
Points Used	Cv 6 Qi Hai	DU 20 Baihui	Liv 3 Taichong	LI 4 Hegu	LI 10 Shoushanli	LU 7 Lieque	SP 6 Sanyinjiao	SP 8 Diji	SP10 Xuehai	ST 28 Shuidao	ST 29 Guilai	ST 36 Zushanli	PC 6 Neiguan	RN 3 Zhongji	RN 4 Guanyuan	RN6 Qihai	K3 Taixi	K11 Henggu	TE5 Weiguan	EX CA1 Zigo +D5: W18ng
Paulus/2002		x	x	x		x	x	x	x		x	x	x							
Smith/2006				x			x	x	x		x	x	x							
Dieterle/2006				x			x	x	x		x	x	x		x	x	x			
Westergaard/2006		x	x	x			x	x			x		x	x						
Domar/2009		x	x	x		x	x	x	x		x	x	x							
So/2009		x	x	x			x	x	x		x	x	x							
Madaschi/2010		x	x	x			x	x	x		x									
So/2010				x			x		x			x								
Moy/2011	x	x	x	x			x	x	x		x	x								
Paulus 2003		x	x	x		x	x	x	x		x	x	x							
Carig 2007	x		x	x			x	x	x		x	x	x				x	x		

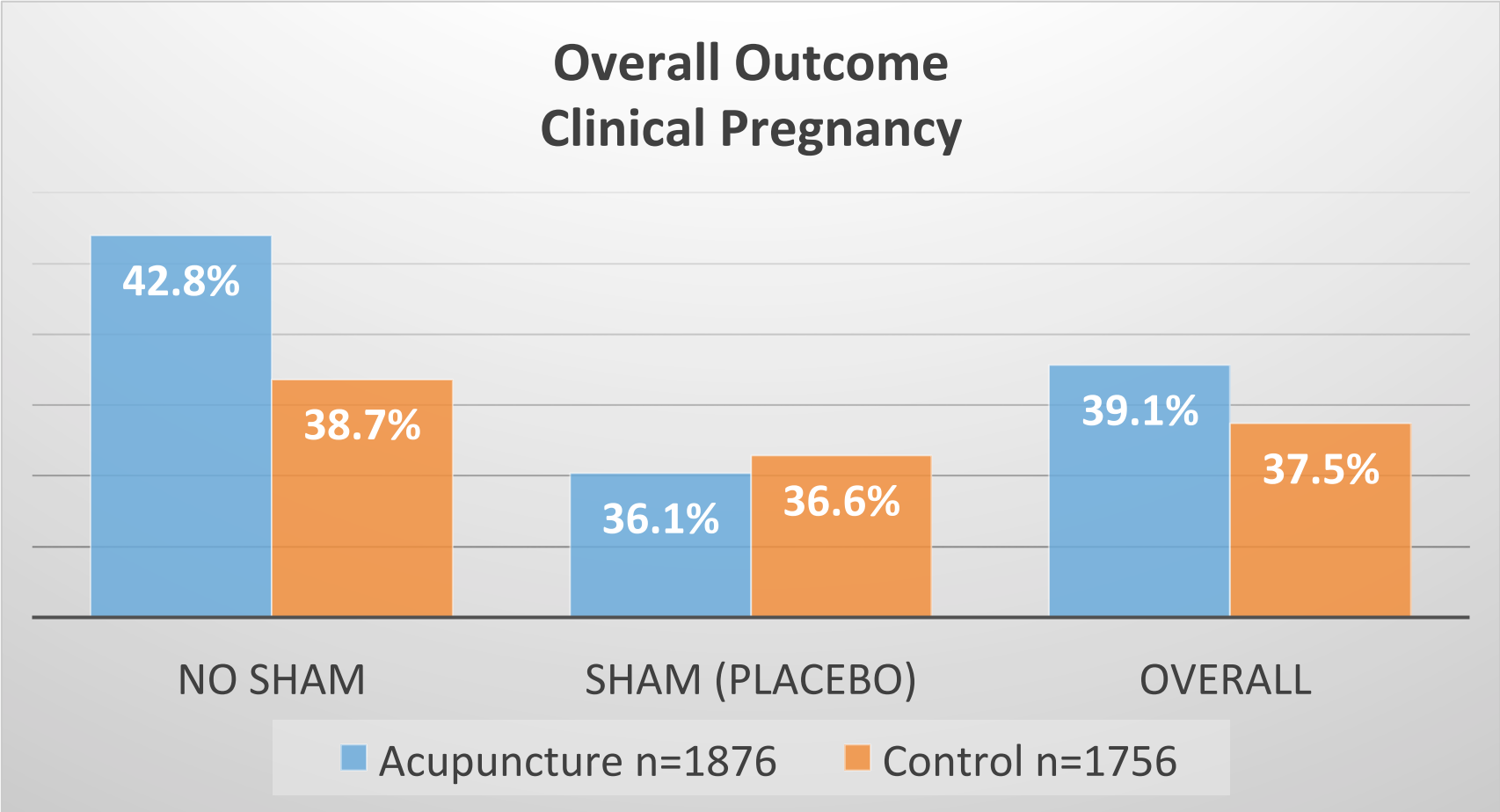
Paulus 2002 vs Domar 2009 vs So 2009

	Paulus 2002	Domar 2009	So 2009
Placebo	no	yes	yes
Pregnancy rate	42.5% vs 26.3%	42% vs 47%	38.9% vs 49.2%
Overall Pregnancy	Unknown	Unknown	35% 2005
Embryo Quality	Good	Good	Unknown

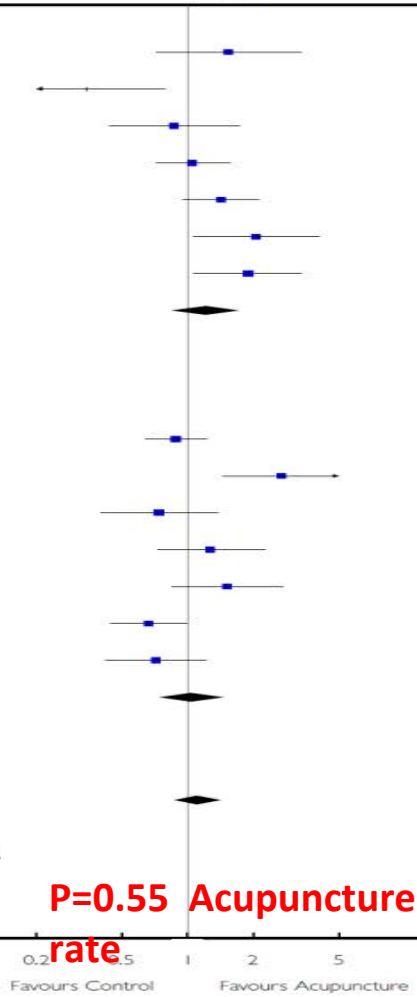

Acupuncture Points Used
2
13
10
16
1
3
14
10
10
1
13
12
8
1
2
2
2
2
1
1
CV 6
DU 20
LIV 3
LI 4
LI 10
LU 7
SP 6
SP 8
SP10
ST 28
ST 29
ST 36
PC 6
RN 3
RN 4
RN6
K3
K11
TE5
EX CA1


Acupuncture on and around the day of ET (No Sham/ Needling)
Clinical Pregnancy
54.7%
44.0%
40.4%
32.2%
42.5%
26.3%
37.6%
24.1%
43.8%
69.6%
30.8%
33.8%
51.5%
50.3%
BENSON 2006 +
MADASCHI 2010 +
PAULUS 2002 +
WESTERGAARD
CRAIG 2007
DOMAR 2009
FRATERELLI 2008
Acupuncture n=853


Acupuncture on and around the day of ET (sham/needling)
Clinical Pregnancy
33.6%
15.6%
43.0%
37.0%
31.2%
22.9%
32.2%
34.9%
45.3%
52.7%
38.9%
49.2%
36.3%
44.2%
DIETERELE 2006
PAULUS 2003
SMITH 2006
ANDERSEN 2010
MOY 2011
SO 2009
SO 2010
Acupuncture n=1876
Control (sham/needling) n=1020


Overall Outcome
Clinical Pregnancy
42.8%
38.7%
36.1%
36.6%
39.1%
37.5%
NO SHAM
SHAM (PLACEBO)
OVERALL
Acupuncture n=1876
Control n=1756

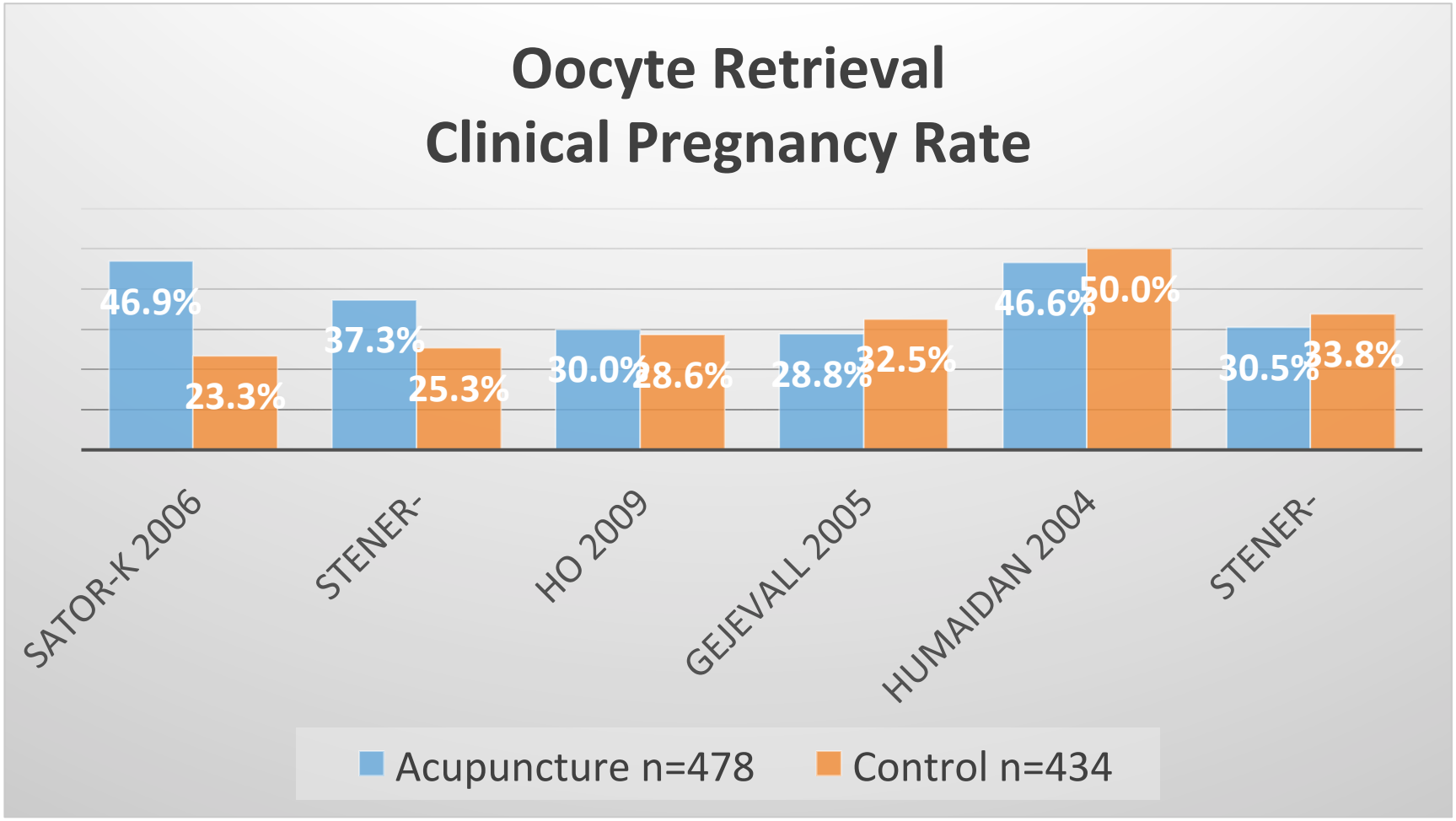
Study or subgroup	Acupuncture n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Acupuncture versus Control (no sham/needling)					
Benson 2006	29/53	22/50		5.3 %	1.54 [0.71, 3.35]
Craig 2007	21/48	32/46		4.8 %	0.34 [0.15, 0.79]
Domar 2009	24/78	23/68		6.0 %	0.87 [0.43, 1.74]
Fraterelli 2008	103/200	99/197		8.9 %	1.05 [0.71, 1.56]
Madaschi 2010	84/208	67/208		8.8 %	1.43 [0.95, 2.13]
Paulus 2002	34/80	21/80		6.2 %	2.08 [1.07, 4.04]
Westergaard 2006	70/186	21/87		7.1 %	1.90 [1.07, 3.37]
Subtotal (95% CI)	**853**	**736**		**47.2 %**	**1.21 [0.84, 1.73]**
Total events: 365 (Acupuncture), 285 (Control)					
Heterogeneity: Tau² = 0.14; Chi² = 15.77, df = 6 (P = 0.02); I² =62%					
Test for overall effect: Z = 1.03 (P = 0.30)					
2 Acupuncture versus Control (sham/needling)					
Andersen 2010	101/314	112/321		9.6 %	0.88 [0.64, 1.23]
Dieterle 2006	39/116	17/109		6.4 %	2.74 [1.44, 5.22]
Moy 2011	39/86	39/74		6.6 %	0.74 [0.40, 1.39]
Paulus 2003	43/100	37/100		7.1 %	1.28 [0.73, 2.26]
Smith 2006	34/109	27/118		6.9 %	1.53 [0.85, 2.76]
So 2009	72/185	91/185		8.7 %	0.66 [0.44, 0.99]
So 2010	41/113	50/113		7.5 %	0.72 [0.42, 1.22]
Subtotal (95% CI)	**1023**	**1020**		**52.8 %**	**1.04 [0.74, 1.46]**
Total events: 369 (Acupuncture), 373 (Control)					
Heterogeneity: Tau² = 0.14; Chi² = 18.79, df = 6 (P = 0.005); I² =68%					
Test for overall effect: Z = 0.22 (P = 0.83)					
Total (95% CI)	**1876**	**1756**		**100.0 %**	**1.11 [0.87, 1.42]**
Total events: 734 (Acupuncture), 658 (Control)					
Heterogeneity: Tau² = 0.14; Chi² = 37.78, df = 13 (P = 0.00031); I² =66%					
Test for overall effect: Z = 0.87 (P = 0.39)					
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² =0.0%					



P=0.55 Acupuncture does not improve pregnancy rate

Oocyte Retrieval
Clinical Pregnancy Rate

Author/Publication Year	Country	Method	Timing of Intervention	Result						
				Clinical Pregnancy	Biochemical Pregnancy	Ongoing Pregnancy	Live Birth Rate	Implantation Rate	Miscarriage Rate	others
Stener-Victorin/ 1999	Sweden	Electroacupuncture	BOR Before Oocyte Retrieval	×	N/A	N/A	○	N/A	×	Reduced stress, pain VAS
Stener-Victorin/ 2003	Sweden	Electroacupuncture	BOR	×	N/A	×	N/A	N/A	×	Reduced stress, pain VAS, Nausea
Humaidan/2004	Sweden	Electroacupuncture	BOR	×	N/A	N/A	N/A	N/A	N/A	Reduced pain VAS
Gejevall/2005	Sweden	Electroacupuncture	BOR	×	N/A	N/A	N/A	N/A	N/A	Reduced stress, pain VAS
Sator-Katzenschager/2006	Austrailia	Electroacupuncture/EA	BOR	○	N/A	N/A	N/A	N/A	N/A	Reduced stress, pain VAS, Nausea


Oocyte Retrieval
Clinical Pregnancy Rate
46.9%
23.3%
37.3%
25.3%
30.0%
28.6%
28.8%
32.5%
46.6%
50.0%
30.5%
33.8%
SATOR-K 2006
STENER-
HO 2009
GEJEVALL 2005
HUMAIDAN 2004
STENER-
Acupuncture n=478
Control n=434

Study or subgroup	Acupuncture n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Acupuncture versus Control					
Gejervall 2005	23/80	26/80		18.4 %	0.84 [0.43, 1.64]
Ho 2009	9/30	4/14		5.9 %	1.07 [0.26, 4.34]
Humaidan 2004	41/88	45/90		21.6 %	0.87 [0.48, 1.57]
Sator-K 2006	30/64	7/30		10.8 %	2.90 [1.09, 7.71]
Stener-Victorin 1999	28/75	19/75		17.5 %	1.76 [0.87, 3.54]
Stener-Victorin 2003	43/141	49/145		25.8 %	0.86 [0.52, 1.41]
Total (95% CI)	**478**	**434**		**100.0 %**	**1.12 [0.78, 1.62]**

Total events: 174 (Acupuncture), 150 (Control)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 7.63$, df = 5 (P = 0.18); $I^2 = 34\%$

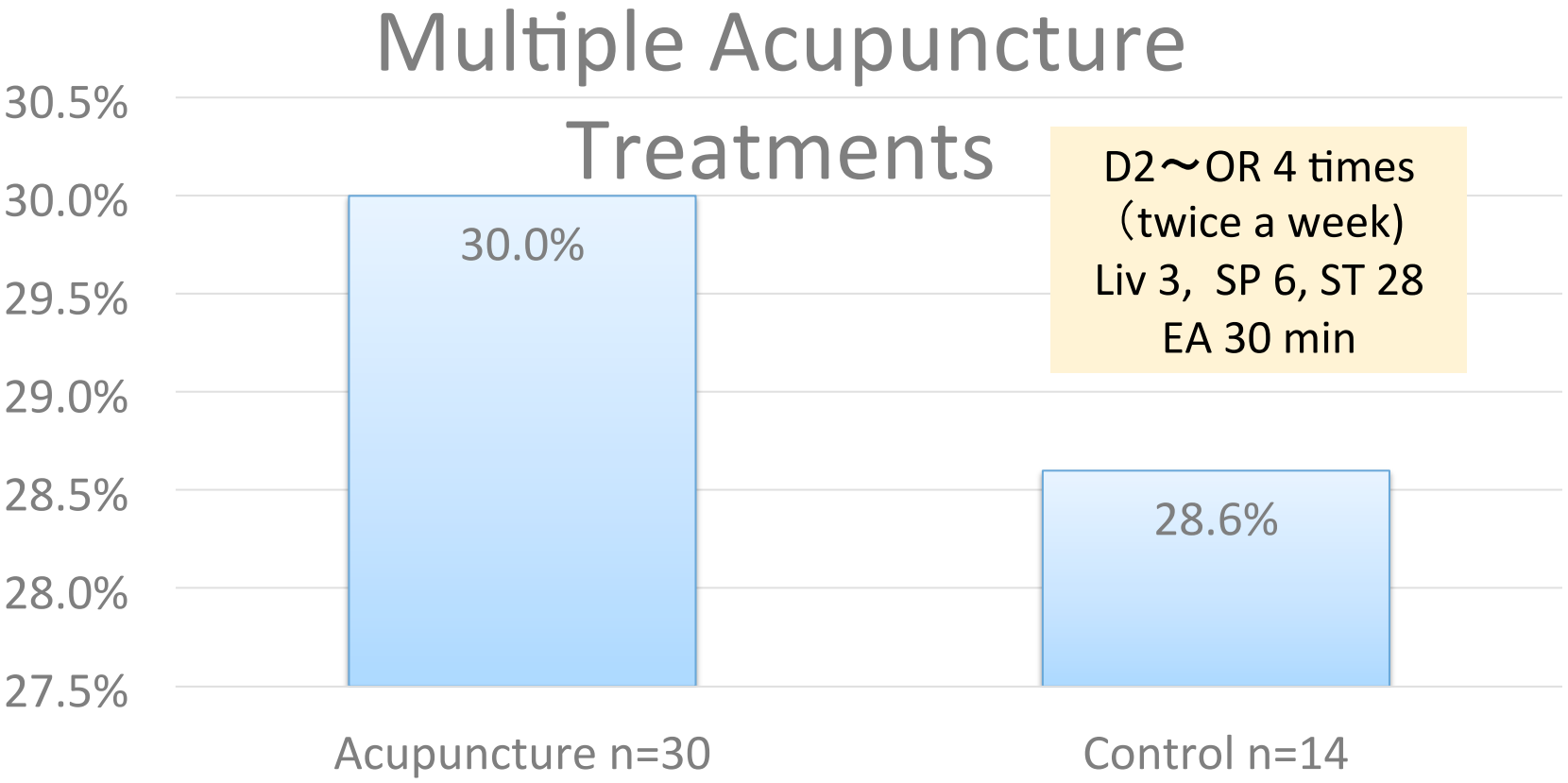
Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

P=0.53 Acupuncture does not improve pregnancy rate

0.1 0.2 0.5 1 2 5 10

Favours Control Favours Acupuncture



Ho 2009

Ho M. Taiwan J Obstetrics and Gynecology 2009;**48**(2):148–

From Cochrane 2009 Repeated acupuncture

Review: Acupuncture and assisted conception

Comparison: 2 Repeated acupuncture versus no acupuncture

Outcome: 3 Clinical pregnancy rate

Study or subgroup	Acupuncture n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Dieterle 2006	39/116	17/109		46.0 %	2.74 [1.44, 5.22]
Westergaard 2006	33/91	21/87		54.0 %	1.79 [0.93, 3.43]
Total (95% CI)	**207**	**196**		**100.0 %**	**2.23 [1.41, 3.51]**

Total events: 72 (Acupuncture), 38 (Control)

Heterogeneity: $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 3.44 (P = 0.00059)

P=0.00059 Acupuncture improves pregnancy rate
However, not enough number and needs further consideration

0.1 0.2 0.5 1 2 5 10

Favours Control Favours Acupuncture

Effectiveness of acupuncture for fertility

1. Change in uterine blood flow and uterine contractility(effects are due to a central inhibition of the sympathetic activity)
2. Relaxation of Stress
3. Effect on the HPO, HPA axis

Variables Which Affect The Outcome Of IVF
体外受精の結果を左右する因子

- Egg Quality (卵子の質）
- Sperm Quality（精子の質）
- Embryo Cultivation Environment（培養環境）
- Endomitrium（内膜の状態）
- Embryo Quality （受精卵の質）
- Implantation Method（移植方法）
- Other factors (その他の因子）

Variables Which Affect Oocyte Quality
卵母細胞の質を左右する因子

- Ovarian Assessment (AMH, Bologna Criteria, Diminished Ovarian Reserve)（卵巣の評価）
- Stimulation Methods (Agoinst, Antagonist, Long, Short, Kato Method)
（刺激法）
- Trigger timing (Oocyte Maturization)（トリガー　成熟卵）
- Oocyte Aspiration Methodolgy（採卵方法）

Author/Publication Year	Assisted Conception Protocol
Paulus/2002	N/A
Smith/2006	N/A
Dieterle/2006	Standard, long, FSH, hMG
Westergaard/2006	Standard, long, FSH, hMG
Domar/2009	N/A
So/2009	Standard, long, FSH, hMG
Madaschi/2010	Standard, long, FSH, hMG
Andersen/2010	Standard, long, FSH, hMG
So/2010	Standard, long, FSH, hMG
Moy/2011	N/A
Paulus 2003	N/A
Carig 2007	N/A
Fraterelli 2008	N/A
Benson 2006	N/A
Stener-Victorin/1999	N/A
Stener-Victorin/2003	N/A
Humaidan/2004	N/A
Gejevall/2005	Standard, long, FSH, hMG
Sator-Katzenschager/2006	N/A
Ho/2009	N/A

Variables Which Affect Sperm and Oocyte Quality（精子と卵子の質を左右する因子）

- Lifestyle
- Alcohol/Cigarettes
- Stress
- Exercise
- Age
- Chromosomal Aberration
- Fresh or Frozen

Embryo Cultivation Environment
培養環境

- Cultivation Medium（培養液）
- Incubator（インキュベータなど、培養環境）
- Skill of Embryologists（培養士の技能・経験）

Endometrium（子宮内膜環境）

- Thickness（内膜の厚さ）
- Immune Tolerance・Implantation Failure（免疫寛容・着床障害）
- Endometrial Receptivity
- Cilia, Pinopode (シリア・ピノポード）
- Vascularity
  - Vasucularity Index（血管の量）
  - Flow Index（血流の速さ）
  - Vascularity Flow Index(血流量）
  - Endometrial Volume（内膜の容積）

Embryo Quality（受精卵の質）

- Embryo Grading（受精卵の評価法）
  - Day 3 Embryo Grading (cell size, fragmentation)
  - Day 5 Embryo Grading (Inner Cell Mass, Trophectoderm Epithelium)
    - Very Early Blastocyst, Expanded Blastocyst, Hatched Blastocyst

Implantation Method（移植法）

- 4-Cell, 8-Cell, Morula, Blastocyst（４分割、桑実胚、胚盤胞）
- Implantation Window (Natural vs Controlled)（着床の窓、自然周期、ホルモン補充周期）
- Frozen vs Fresh（新鮮胚、凍結胚）
- Hormone Supplementation（ホルモン補充の有無）

Other factors（その他の因子）

- Age 年齢
- Previous treatment history 不妊治療歴
  - Oocyte retrival and Embryo transfer history (採卵歴及び移植歴）
- BMI

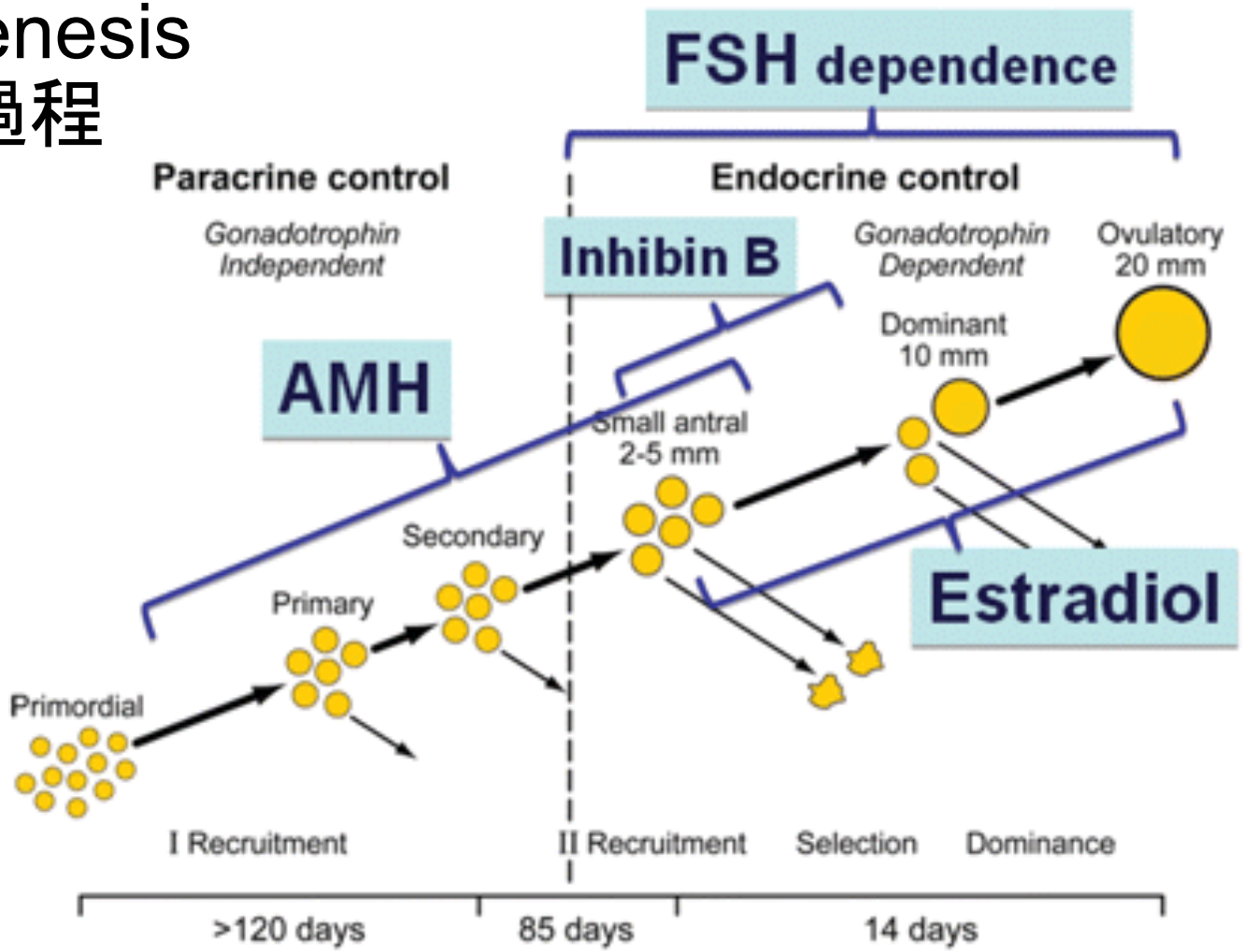
Outcome of IVF…Not Just Acupuncture
IVFの結果を左右する因子、、、鍼以外に沢山ある

- There are several variables that affect the outcome of IVF（体外受精の結果に影響を与える因子が多数存在）
- In order to assess the true efficacy of acupuncture, further consideration necessary.（鍼の真の効果を測定するには、それらの因子の扱い方に注意が必要）

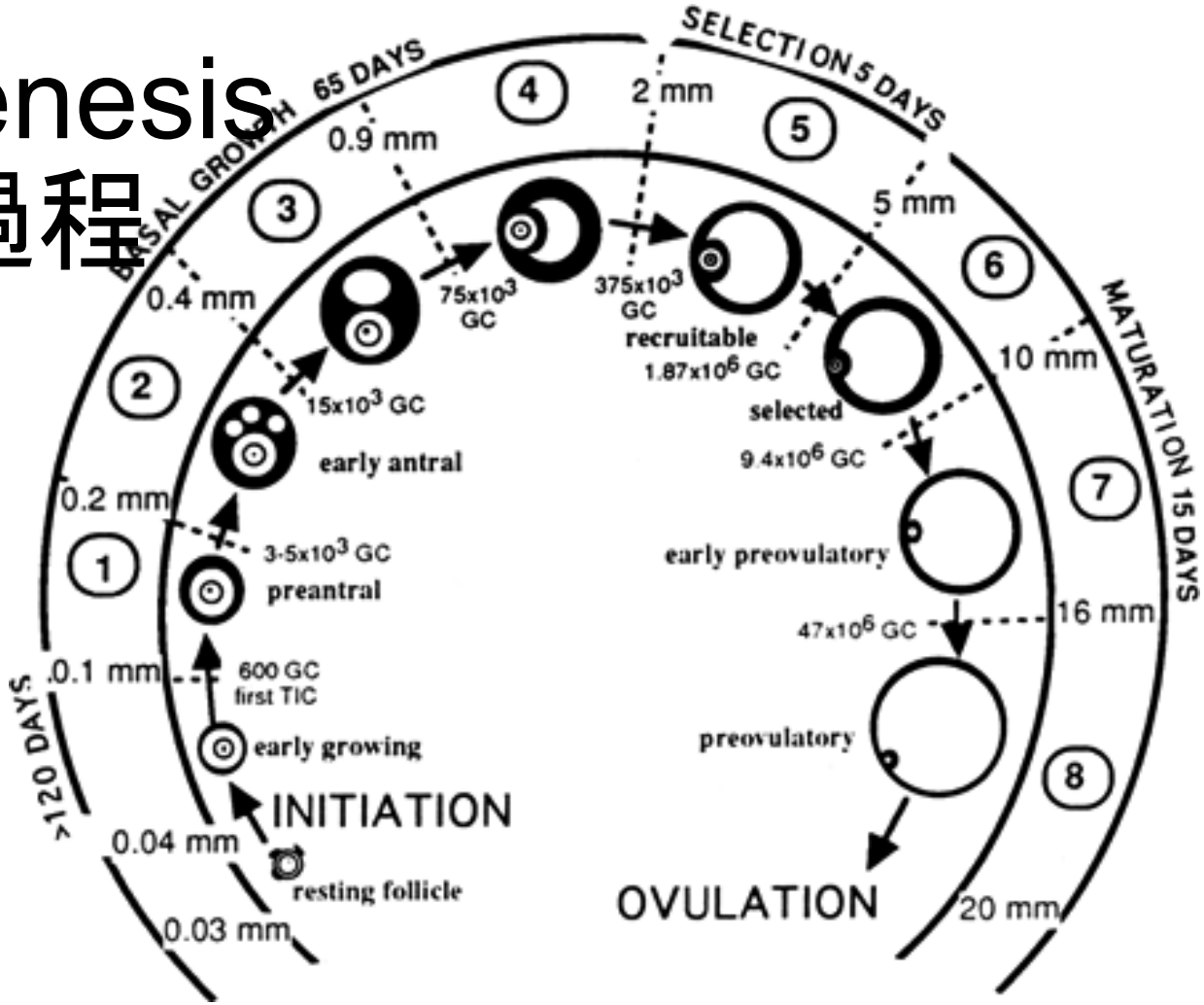
Quality Improvement of Oocyte
卵母細胞の質の向上

- How long should it take to improve the quality of Oocyte theoretically? （質の向上をために、どれぐらいの期間を要するのか？）

Folliculogenesis
卵胞形成過程



Folliculogenesis
卵胞形成過程



Discussion

- How can we successfully measure the effectiveness of acupuncture in reproductive medicine?（鍼の効果を確実に測定する方法とは？）

  1. Endometrial Plasticity
  2. Immune Tolerance
  3. PGD/PGS (Aneupolidy, Chromosomal Aberration)
  4. Finding optimum control (Placebo/Sham)