

**Poor response cycles:
when should we cancel?**
Comparison of outcome between
egg collection,
intrauterine insemination,
conversion,
and follow-up cycles after
abandonment

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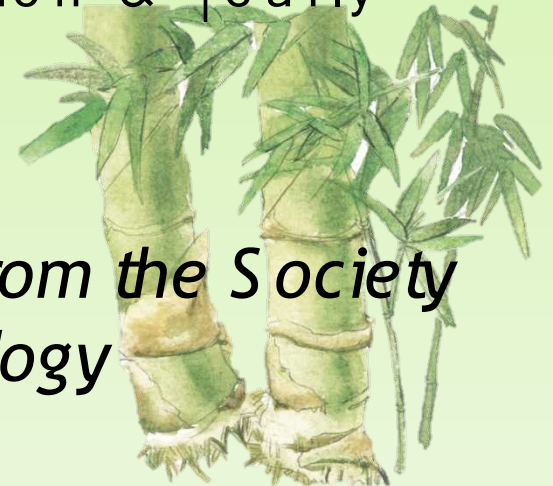
2011

Presenter: R 2 孫怡虹

2011-02-15

Introduction

- ↑ average age of natural childbirth ↔
↑ proportion of women entering into fertility treatment at a later age (last decade)
- **Maternal age** – The significant factor associated with ↓ odds of conception & ↑ early pregnancy loss
 - *Analysis of 15 years of UK data*
 - *Multivariate analysis of US data from the Society of Assisted Reproductive Technology*



- **Several markers** (age-related effect on ovarian reserve that drives this decline)
 - Predictors of ART pregnancy outcome
 - Limited accuracy
 - More appropriately be used to assess the risk of cycle cancellation



- **Pre-cycle ultrasound markers** of ovarian reserve
(*A meta-analysis of the diagnostic accuracy*)

- **Antral follicle count** < 4

- Predict cycle cancellation

- Sensitivity: 66.7% ; specificity: 94.7%

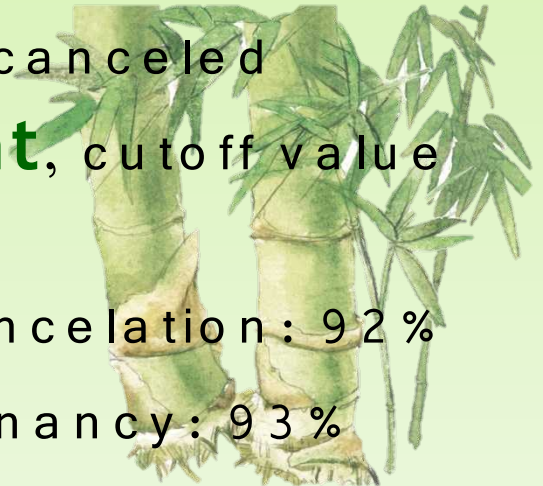
- 8.7 x less likely to get pregnant after IVF

- 37 x more likely to have their cycle canceled

- **Ovarian volume measurement**, cutoff value
3 cm³

- Specificity for prediction of cycle cancellation: 92%

- Specificity for prediction of nonpregnancy: 93%



- **Pre-cycle serologic markers** of ovarian reserve (inhibin -B , FSH , and anti-Müllerian hormone [AMH])

(A systematic review)

→ Accurate at predicting poor response and nonpregnancy only at **very high thresholds**

→ Predominantly for counseling only

→ A first IVF attempt may often be the step of choice for diagnostic purposes



- **Pericycle markers** of ovarian reserve
 - Follicle number during ovarian stimulation
 - Number of oocytes collected
- Seem to correlate with cycle success



- *Whether to continue with egg collection or cancel a cycle?*
- Is often difficult
- Encompassing emotional, logistic, financial, and clinical considerations
- Based on little published data



An analysis of ART cycles

- with 1 or 2 mature follicles after ovarian stimulation
- when the decision to cancel is most often faced
- To compare outcomes of cycles:
 - Proceed to vaginal egg collection (VEC)
 - Convert to intrauterine insemination (IUI)
 - Subsequent cycles in those who decide to abandon their cycle

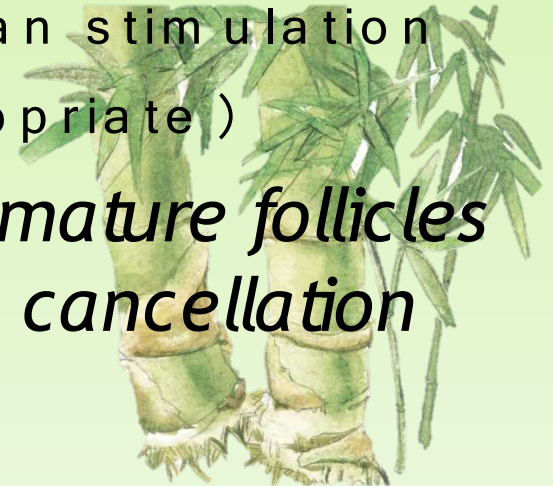




MATERIALS AND METHODS

- Collected data prospectively
 - Retrospective search of the database
- January 1998 ~ June 2009
- Identify ovarian stimulation cycles for IVF and intracytoplasmic sperm injection (ICSI)
- 1 or 2 follicles >12 mm after ovarian stimulation (when hCG trigger would be appropriate)

Operator could enter the number of mature follicles achieved before trigger or cycle cancellation



- 3 groups

(According to the decision made after counseling by nursing and medical staff at the time of optimal follicle maturity)

- Group 1 : Who decided to proceed to V E C
- Group 2 : decided to convert to I U I
- Group 3 : decided to abandon the current cycle



Long protocol

• **GnRH-analogue** (Injectable or Nasal)

- Midluteal phase or M C day 1
- Preceded by a priming phase using the combined O C P in some cycles, depending on clinical grounds and clinician choice

Cetrorelix protocol

• **GnRH hormone antagonist**

- Leading follicle reached 12 m m



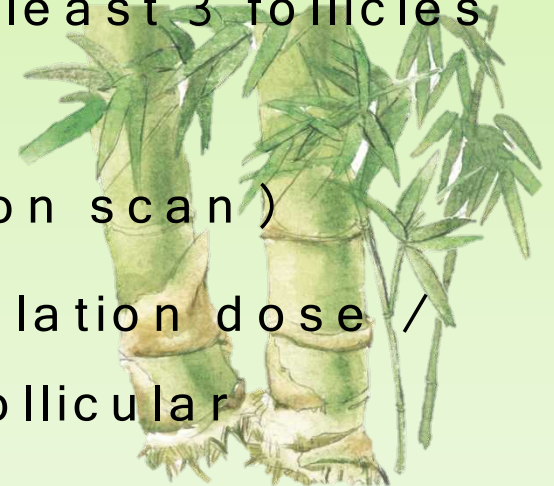
Treatment Protocol

Transvaginal scan

- Before ovarian stimulation → ensure ovarian quiescent
- After 5 ~ 6 days of stimulation → 1st stimulation scan
- Every 24–72 hours thereafter → At least 3 follicles >18 mm

Estradiol levels (with every stimulation scan)

- Determine appropriateness of stimulation dose / Dose adjustment (association with follicular response)



Estradiol levels

At initial stimulation scan (day 5 to 6)

- 1,500 ~ 3,000 pmol/L => continuation of the current dosing regimen
- <1,500 pmol/L => increase of 75 IU/d
- >3,000 pmol/L => decrease of 75 IU/d



Estradiol levels

Before hCG administration (when follicles reached a preovulatory size of 18–22 mm)

- Standard operating procedure target

- >2,000 pmol/L

- Approximately 500 pmol/L per good follicle

- Upper limit of 15,000 pmol/L before coasting adopted



Treatment Protocol

- Ovarian stimulation: r-FSH, r-hMG, or urinary

Early cycle FSH	<10 IU/L		>10 IU/L
Starting doses (IU /d)	< 35 y/o	> 36 y/o	
no PCO	225	300	300– 450
Polycystic ovarian syndrome (PCOS) or Hx of PCO-like response	100– 150	150– 225	
PCO & Hx of OHSS	75–100	100– 150	

- hCG administration

→ (34–36 hrs) Oocytes aspirated /TVS guidance →
(D 2, 3, or 5) Embryo transfer /embryo quality
and quantity, soft catheter, TAS guidance →
(2 wks after ET) pregnancy test

→ (36 hrs) Insemination (converted to IUI)

- P (400 mg) pessaries (All patients)

→ Throughout the luteal phase → continued to 8–
10 weeks of pregnancy



Outcome Measures and Statistical Analysis

- 1^o outcome:
 - live birth rate (LBR)
- 2nd outcomes:
 - Clinical pregnancy rate (viable intrauterine pregnancy confirmed on first-trimester ultrasound scan; CPR)
 - Biochemical pregnancy rate (serum- or urinary-positive pregnancy test; BPR)



- Group 1 data: outcome per egg collection
- Group 2 data: outcome per insemination, and
- Group 3 data: outcome per cycle abandoned (as denominator) in 1st subsequent cycle of assisted reproduction performed (excluding abandoned cycles with <6 months' f/u)



- *Shapiro-Wilk W test of normality* → Distribution
- *Mann-Whitney test or Kruskal-Wallis analysis of variance* → Comparison of continuous variables (such as maternal age or gonadotropin use) between groups
- *Fisher's exact test and χ^2 test* → Group effect on BPR, CPR, and LBR
- Analyse - It statistical software for Excel (Microsoft, Redmond, WA)



RESULTS



Endpoint of cycles commenced with
 ≤ 2 follicles at decision to trigger

Endpoint	Total (≤ 2 follicles)	1 follicle	2 follicle
Total cycles	1,350 (7.3%)	524	826
Abandoned	295 (21.9) ^a	180 (34.4) ^a	115 (13.9) ^a
Converted to IUI	248 (18.4) ^a	120 (22.9) ^a	128 (15.5) ^a
Proceed to VEC	807 (59.8) ^a	224 (42.7) ^a	583 (70.6) ^a
No eggs collected/ degenerating eggs only	94 (11.6) ^b	37 (16.5) ^b	57 (9.8) ^b
Failed fertilization	121 (15.0) ^b	48 (21.4) ^b	73 (12.5) ^b
Fertilization/no ET	61 (7.6) ^b	17 (7.6) ^b	44 (7.5) ^b
Embryos frozen/no transfer	3 (0.4) ^b	0	3 (0.5) ^b
ET cycles	522 (64.7) ^b	122 (54.5) ^b	400 (68.6) ^b

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Converted to IUI G 2	248 (18.4) ^a	120 (22.9) ^a	128 (15.5) ^a
Proceed to VEC G 1	807 (59.8) ^a	224 (42.7) ^a	583 (70.6) ^a
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h C G
trigger

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hCG trigger

Fisher's all P < .05



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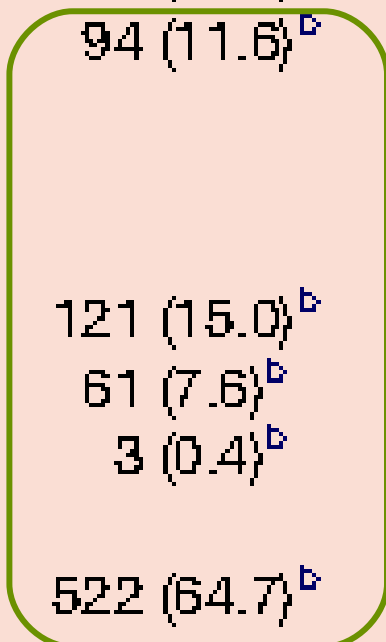
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hCG trigger



Fisher's P < .05



<

Endpoint of cycles commenced with
 ≤ 2 follicles at decision to trigger

Endpoint	Total (≤ 2 follicles)	1 follicle	2 follicle
Egg collection	2.1	1.3	2.3
Proceed to VEC G1	807 (59.8) ^a	224 (42.7) ^a	583 (70.6) ^a
No eggs collected/ degenerating eggs only	94 (11.6) ^b	37 (16.5) ^b	57 (9.8) ^b
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hCG trigger

ET: 1.4

Cycle details and outcome by decision groups

Parameter	Group 1 (VEC)	Group 2 (IU)	Group 3 (abandoned)	P value
Total cycles	800	247	279	
Maternal age (y)	39.6 ± 3.9 (40) >	39.3 ± 3.9 (40) >	38.6 ± 4.4 (39)	<.01 ^a
AMH (pmol/L)	4.0 ± 4.3 (2.9)	4.8 ± 6.7 (2.3)	3.5 ± 3.5 (2.1)	.65 ^a
FSH (IU/L)	11.9 ± 7.8 (10.0)	11.2 ± 7.2 (9.3)	11.4 ± 7.7 (9.4)	.18 ^a
Total gonadotropins (IU)	4,229 ± 2,209 (4,125) >	3,520 ± 1,517 (3,375) >	3,272 ± 1,703 (3,150)	<.01 ^a
Gonadotropins/d (IU/d)	381 ± 301 (380)	362 ± 341 (310)	338 ± 243 (333)	<.01 ^a
Biochemical pregnancy	13.1% (105/800)	4.9% (12/247)	9.7% (27/279)	<.01 ^b
Clinical pregnancy	8.1% (65/800)	3.6% (9/247)	7.2% (20/279)	.05 ^c
Ongoing pregnancy	6.8% (54/800)	2.0% (5/247)	5.4% (15/279)	.02 ^b
				.10 ^c
				<.01 ^b
				.07 ^c

Kruskal-Wallis P <.05

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AMH (pmol/L)	4.0 ± 4.3 (2.9)	4.8 ± 6.7 (2.3)	3.5 ± 3.5 (2.1)	.55 ^a
FSH (IU/L)	11.9 ± 7.8 (10.0)	11.2 ± 7.2 (9.3)	11.4 ± 7.7 (9.4)	.18 ^a

no difference in precycle markers of ovarian reserve

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Clinical pregnancy	8.1% (65/800)	>	3.6% (9/247)	<	7.2% (20/279)	.02 ^b .10 ^c
Ongoing pregnancy	6.8% (54/800)	>	2.0% (5/247)		5.4% (15/279)	<.01 ^b .07 ^c

Mann-Whitney P <.05

Cycle details and outcome by decision groups

groups

16 were excluded from analysis (<6-month f/u period)
 146 (52.3%) subsequent cycle(s)
 80, 37, 17, 6, 5, 1 ↔ 1~6 further cycles

- 1st subsequent cycle:
 - ⇒ 4.4 mean egg collection
 - ⇒ 103 (70.5%) proceeded to ET
 - ⇒ 2.0 mean ET
 - ⇒ **O**ngoing **P**regnancy **R**ate: 10.3%
- all subsequent cycles:
 - ⇒ **C**umulative **C**PR: 12.5%

Group 3 (abandoned)	P value
279	
38.6 ± 4.4 (39)	<.01 ^a
3.5 ± 3.5 (2.1)	.65 ^a
11.4 ± 7.7 (9.4)	.18 ^a
3,272 ± 1,703 (3,150)	<.01 ^a
338 ± 243 (333)	<.01 ^a
9.7% (27/279)	<.01 ^b
	.05 ^c
7.2% (20/279)	.02 ^b
	.10 ^c
5.4% (15/279)	<.01 ^b
	.07 ^c

Cycle outcome by decision groups subdivided by follicle number

Variable	Group 1 (VEC)		Group 2 (IUI)		Group C (abandoned)	P value
One follicle						
Biochemical pregnancy	8.5 (19/223)		5.8 (7/120)		5.3 (9/169)	NS ^{a-c}
Clinical pregnancy	5.4 (12/223)		5.0 (6/120)		3.6 (6/169)	NS ^{a-c}
Ongoing pregnancy	4.5 (10/223)		2.5 (3/120)		2.4 (4/169)	NS ^{a-c}
Two follicles						
Biochemical pregnancy	14.9 (86/577)	>	3.9 (5/127)	<	16.4 (18/110)	<.01 ^a .79 ^b <.01 ^c
Clinical pregnancy	9.2 (53/577)	>	2.4 (3/127)	<	12.7 (14/110)	.01 ^a .32 ^b <.01 ^c
Ongoing pregnancy	7.6 (44/577)	>	1.6 (2/127)	<	10.0 (11/110)	<.01 ^a .50 ^b <.01 ^c



DISCUSSION

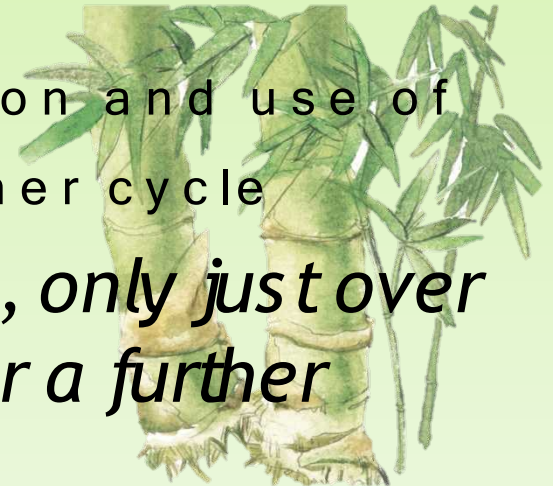
In cycles with 1 or 2 follicles after ovarian stimulation

- The chances of achieving successful pregnancy are best with proceeding to hCG trigger and VEC

- **Significantly** lower pregnancy outcome is seen with conversion to IUI

- No benefit overall in cycle cancellation and use of the experience gained to plan a further cycle

- *of whom abandoned their cycle, only just over half (52.3% ; n= 146) returned for a further cycle*



- Age, follicle number, and gonadotropin use seem to play a role in the decision-making process



Follicle number

- one-follicle cycles might be the most likely to benefit from proceeding to VEC
 - The **perceived poor outcome** with one follicle compared with two follicles leads significantly more couples to abandon their cycle
- ⇒ After correct to assume a poorer initial outcome with one follicle (LBR of 7.6% vs. 4.5%)
- ⇒ **similar proportion** of abandoned one- and two-follicle couples **return** for future cycles (47% and 53%)



Age

- Ovarian reserve (indirectly measured by age and gonadotropin requirements) → encourage a proactive approach, with a higher likelihood of proceeding to IUI and IVF

$\geq 40y/o$	BP R	CP R	LB R
per egg collection	9.0 %	4.5 %	3.6 %
per abandoned cycle (39% returning)	4.2 %	2.1 %	0.7 %

Decision to cancel a cycle

- Incorporates emotional, financial, and clinical considerations, and in a situation of poor response
- 1st – The realization of the **poor potential outcome** in conjunction with the **potential financial burden** → abandon and consider other treatment modalities or adoption services secondly
- 2nd – Perceived possibility of an improved response in future cycles as a consequence of a tailored treatment protocol



- Careful counseling :

with one or two follicles that, although response and therefore pregnancy outcome might be suboptimal,

proceeding to VEC might remain their best chance of success, particularly with increasing age.





**THANK YOU FOR
LISTENING**