Dr Karen Buckingham

Obstetrician and Gynaecologist

Repromed

Dr Devashana Gupta

Repromed

Auckland

Saturday, June 10, 2017 (Room 1)

8:30 - 9:25 WS #93: Optimising Fertility - Periconception Management

9:35 - 10:30 WS #105: Optimising Fertility - Periconception Management (Repeated)

repromed

Fertility excellence with heart

Optimising Fertility
Periconception Management

Rotorua GP CME

June 2017

Dr Karen Buckingham

Case 1

32 year old Sadie comes along to see you as she is very concerned that she hasn't conceived after 3 months of "trying".

What do you advise?

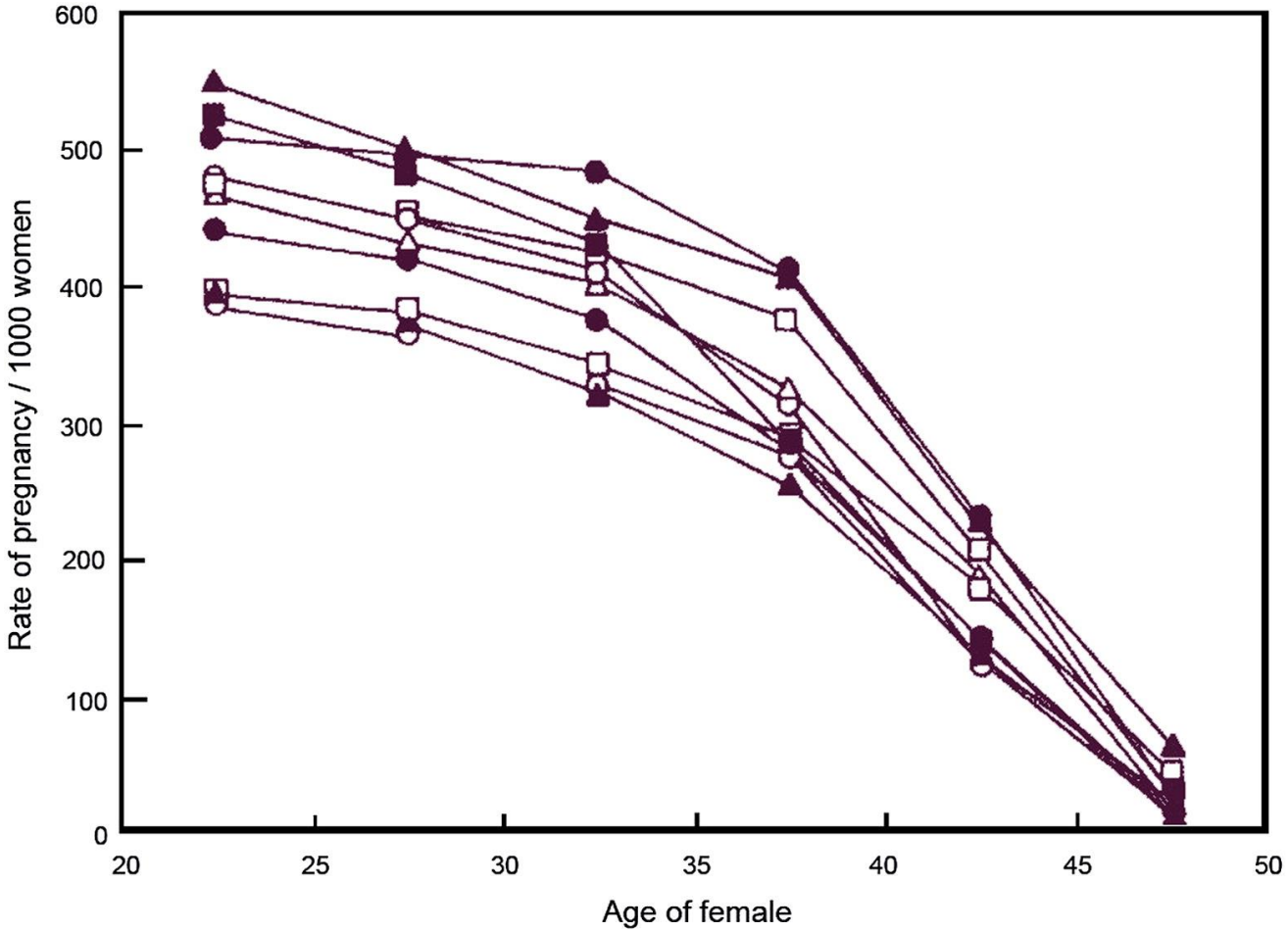
What is normal natural fertility?

- Among apparently normal couples:
  - 80% conceive within 1st 6 months
  - 85% conceive within 1 year
  - 95% conceive within 2 years
- "Fecundability" decreases over time and with increasing age of the female partner

Age (Years)	% Monthly Fecundity
25	25%
30	20%
35	16%
37	11%
40	6%
42	4%
44	2%

reproMED
Fertility excellence with heart

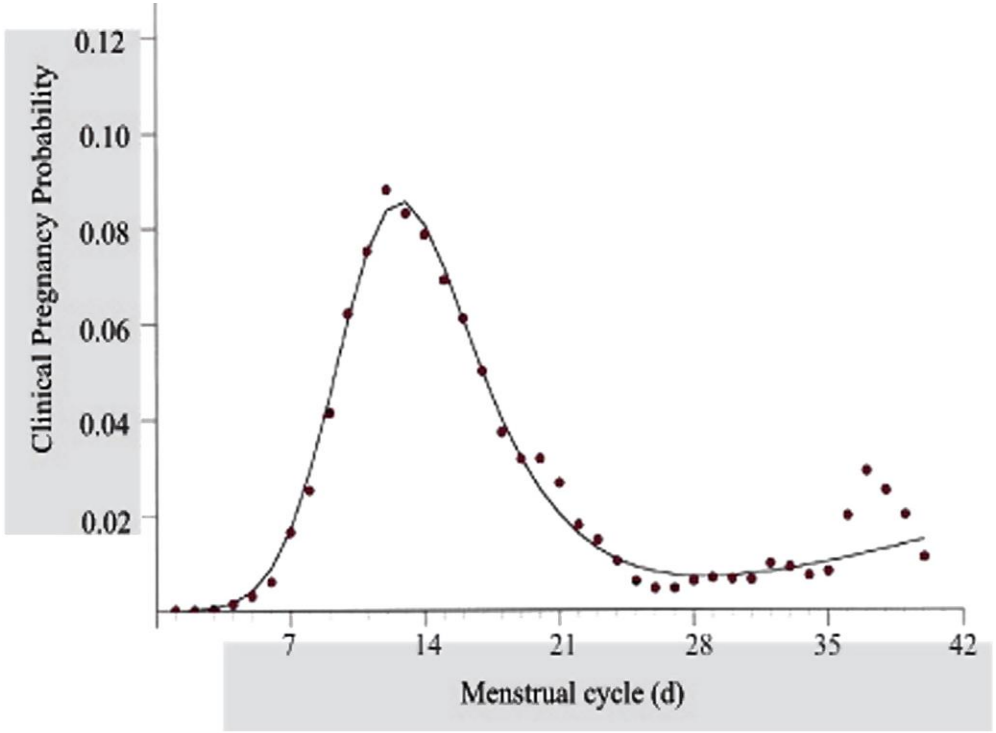
How does age affect fertility?

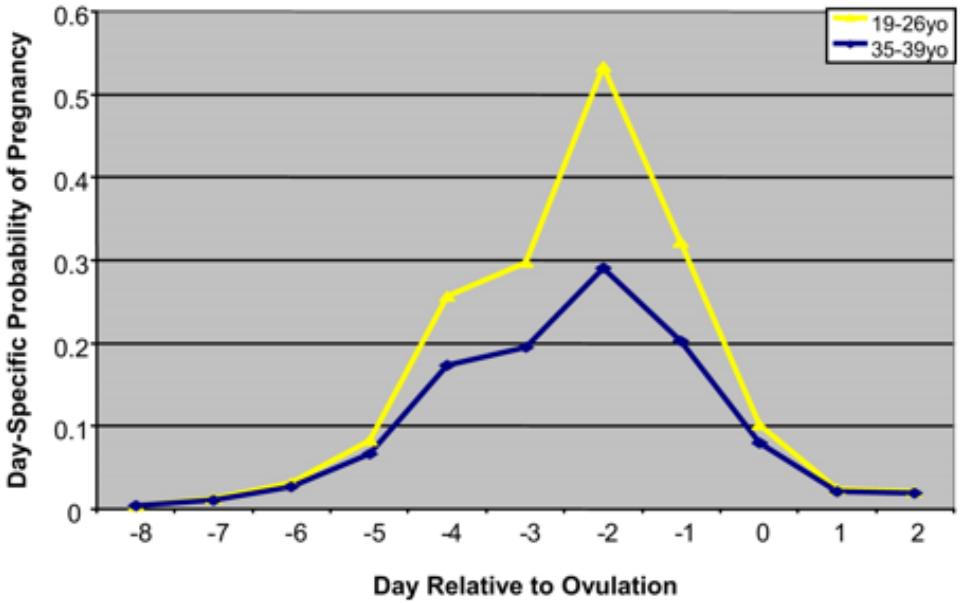


Fertility and Sterility 2013 100, 631-637DOI

reprOmed
Fertility excellence with heart

When is the fertile window of the cycle?





Fertility and Sterility 2013 100, 631-637

- Fertile interval in each cycle is ~6 days in length → 5 days prior to ovulation + day of ovulation
- Highest probability of conception occurs when intercourse takes place 1-2 days prior to ovulation and on day of ovulation.

reproMED
Fertility excellence with heart

Identifying the “fertile window”

- Ovulation predictors may be particular helpful for women with irregular cycles or couples who have infrequent intercourse
- No substantial evidence that self monitoring to predict ovulation increases cycle fecundability

reproMED
Fertility excellence with heart

Coital practices…..

- Optimal coital frequency → regular intercourse 2-3 x week beginning soon after cessation of menses will ensure intercourse falls within the fertile period and semen quality is optimal

- Effect of lubricants → no compelling data to suggest that lubricant use impairs fertility in vivo. Probably prudent to use lubricants that do not inhibit sperm motility if needed e.g. Pre-Seed, mineral oil, canola oil

- Coital position, presence or absence of female orgasm and female position (eg remaining supine) after ejaculation do not appear to affect the likelihood of conception.

Optimise Weight

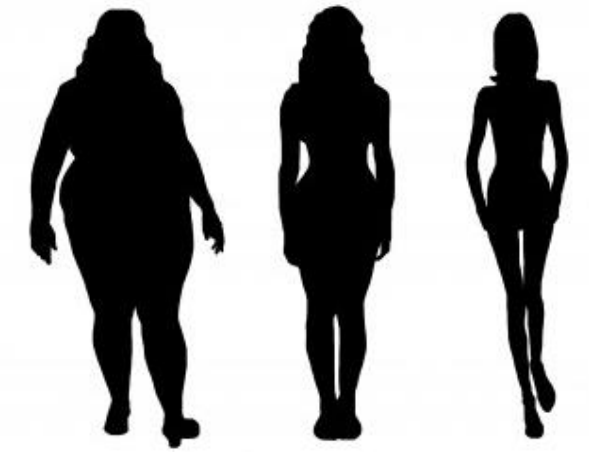
Overweight/Obese

- ↑ ovulatory dysfunction, impaired semen quality, ↓ libido, erectile dysfunction
- ↑ time to conception and infertility
- Poorer outcomes from IVF
- ↑risk of adverse maternal and infant health outcomes

- ***Women must have a BMI <32 to be eligible for publicly funded fertility treatment***

Underweight

- ↑ ovulatory dysfunction, time to conception and infertility
- ↑IUGR, pre-term delivery and low birth weight infants



reprOmed
Fertility excellence with heart

Modify Exercise Practice

- Reasonable to assume that the general health benefits associated with moderate levels of exercise would also apply to fertility

- Female fertility can be adversely affected by increased intensity and duration of exercise
  - The specific type of exercise does not appear to be a factor
  - Women with BMI <25 should limit vigorous exercise to <5 hours/week
  - One study showed that in women undergoing IVF, ≥4 hours of strenuous exercise/week was associated with poorer outcomes

- Male fertility does not appear to be affected by exercise

reproMED
Fertility excellence with heart

Advise Smoking Cessation

- Not only for overall health benefits but also to:
  - ↓ risk of subfertility and time to pregnancy
  - ↑ success from IVF
  - ↓ miscarriage/ectopic pregnancies/preterm birth/low birth weight
  - Prevent damage to fetal ovaries/testes

- Subfertility associated with smoking can be reversed within a year of cessation.

- ***Women who smoke are ineligible for publicly funded treatment (women need to have been non-smokers for at least 3 months)***

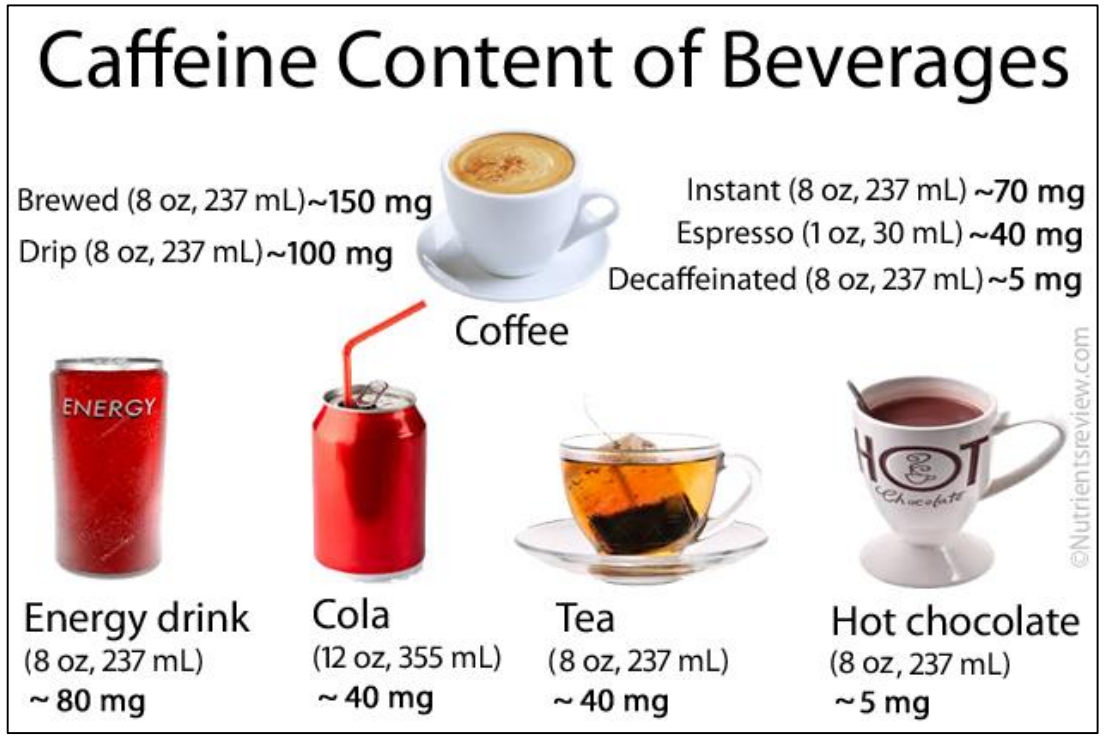
reprOmed
Fertility excellence with heart

Limit Alcohol

- Observational data suggest mod/heavy drinkers (defn vary):
  - ↑ risk of subfertility, time to pregnancy, miscarriage
  - Abnormal testicular function, ↓ testosterone, ↓ libido, erectile dysfunction, ↓ spermatogenesis
  - ↓ IVF success rates
- Evidence less clear for consumption of lower levels of alcohol
- Abstinence at conception/during pregnancy is recommended because a safe level of prenatal alcohol consumption has not been established.

reprOmed
Fertility excellence with heart

What about Caffeine?



- >5 cups coffee/day associated with ↓ fertility
- >2-3 cups coffee/day during pregnancy associated with ↑ miscarriage
- Suggest women who are attempting to conceive or who are pregnant or breastfeeding limit caffeine consumption to <200-300 mg per day.
- No strong evidence to support limiting caffeine intake in the male partner

reproMED
Fertility excellence with heart

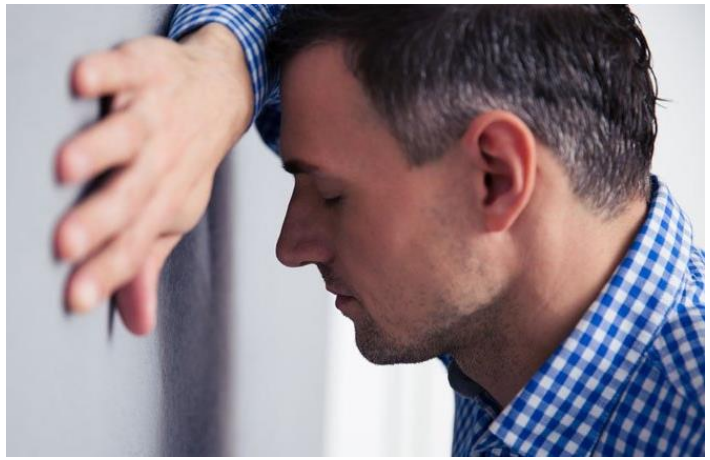
Recreational drug use

- The effects of marijuana and other recreational drugs on fertility are difficult to determine because their use is illegal.

- Drug use should be discouraged for both men and women as they have well documented harmful effects on the developing fetus.

reproMED
Fertility excellence with heart

What about stress?

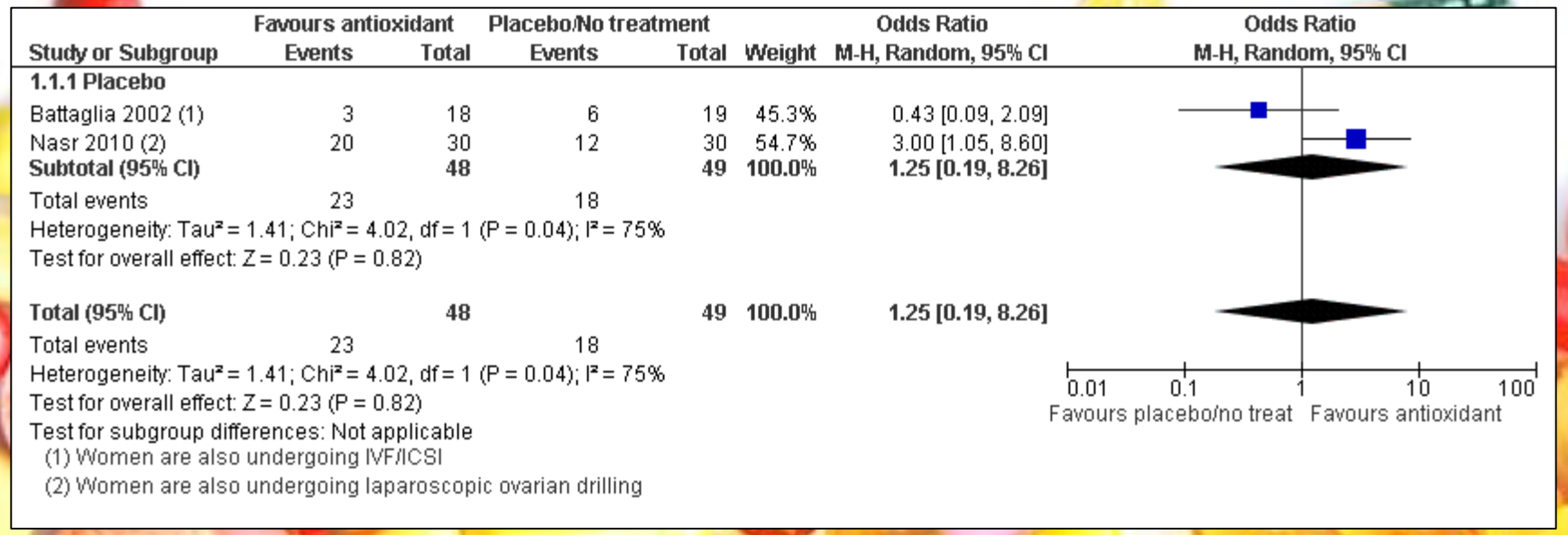


- Infertile women experience high levels of stress…….does stress ↑ risk of infertility?
- Level of stress tends to ↑ as treatment intensifies and as duration lengthens
- No evidence that stress levels influence the outcome of fertility treatment, except to contribute to patients' decisions to discontinue treatment.
- Psychological interventions may decrease psychological symptoms and improve pregnancy rates.

repromed
Fertility excellence with heart

What about supplements/vitamins for women?

- Recommend folic acid/iodine
- Antioxidants were not found to be effective for increasing rates of live birth or clinical pregnancy.



Study or Subgroup	Favours antioxidant Events	Total	Placebo/No treatment Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Placebo						
Battaglia 2002 (1)	3	18	6	19	45.3%	0.43 [0.09, 2.09]
Nasr 2010 (2)	20	30	12	30	54.7%	3.00 [1.05, 8.60]
Subtotal (95% CI)		**48**		**49**	**100.0%**	**1.25 [0.19, 8.26]**
Total events	23		18			
Heterogeneity: Tau² = 1.41; Chi² = 4.02, df = 1 (P = 0.04); I² = 75%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**48**		**49**	**100.0%**	**1.25 [0.19, 8.26]**
Total events	23		18			
Heterogeneity: Tau² = 1.41; Chi² = 4.02, df = 1 (P = 0.04); I² = 75%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Test for subgroup differences: Not applicable						

(1) Women are also undergoing IVF/ICSI

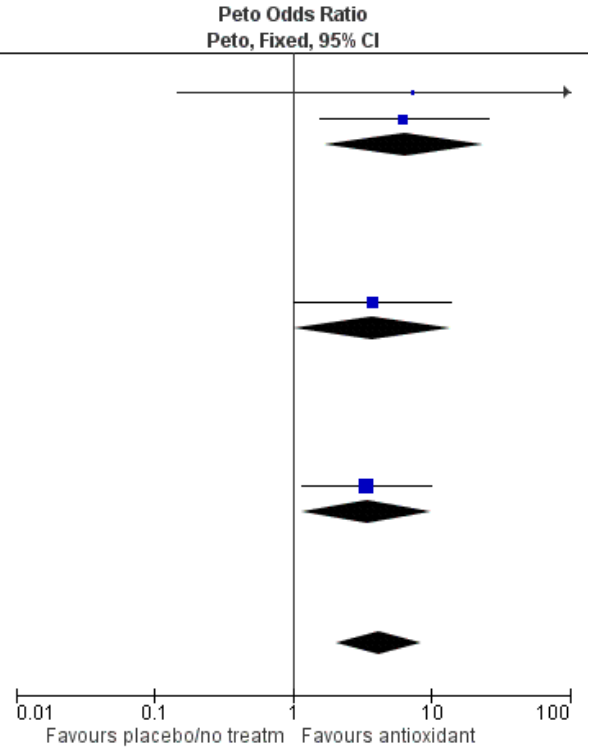
(2) Women are also undergoing laparoscopic ovarian drilling

Cochrane Database of Systematic Reviews August 2013

What about supplements/vitamins for men?

- Limited data showing antioxidants can increase live birth rates in subfertile men

Study or Subgroup	Antioxidant Events	Total	Placebo or no treatment Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Vitamin E versus placebo						
Kessopoulou 1995 (1)	1	15	0	15	3.2%	7.39 [0.15, 372.38]
Suleiman 1996 (2)	9	52	0	35	25.4%	6.33 [1.56, 25.63]
Subtotal (95% CI)		**67**		**50**	**28.6%**	**6.44 [1.72, 24.04]**
Total events	10		0			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.77 (P = 0.006)						
1.1.2 Zinc versus no treatment						
Omu 1998 (3)	8	50	2	50	29.4%	3.74 [1.02, 13.74]
Subtotal (95% CI)		**50**		**50**	**29.4%**	**3.74 [1.02, 13.74]**
Total events	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.1.3 Combined antioxidants versus placebo						
Tremellen 2007 (4)	20	40	4	20	42.0%	3.42 [1.15, 10.13]
Subtotal (95% CI)		**40**		**20**	**42.0%**	**3.42 [1.15, 10.13]**
Total events	20		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
Total (95% CI)		**157**		**120**	**100.0%**	**4.21 [2.08, 8.51]**
Total events	38		6			
Heterogeneity: Chi² = 0.58, df = 3 (P = 0.90); I² = 0%						
Test for overall effect: Z = 4.00 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.57, df = 2 (P = 0.75), I² = 0%						



Footnotes

(1) Undergoing IVF.

(2) Unable to use ITT as it was unknown from which group the 23 were lost from. Natural conception.

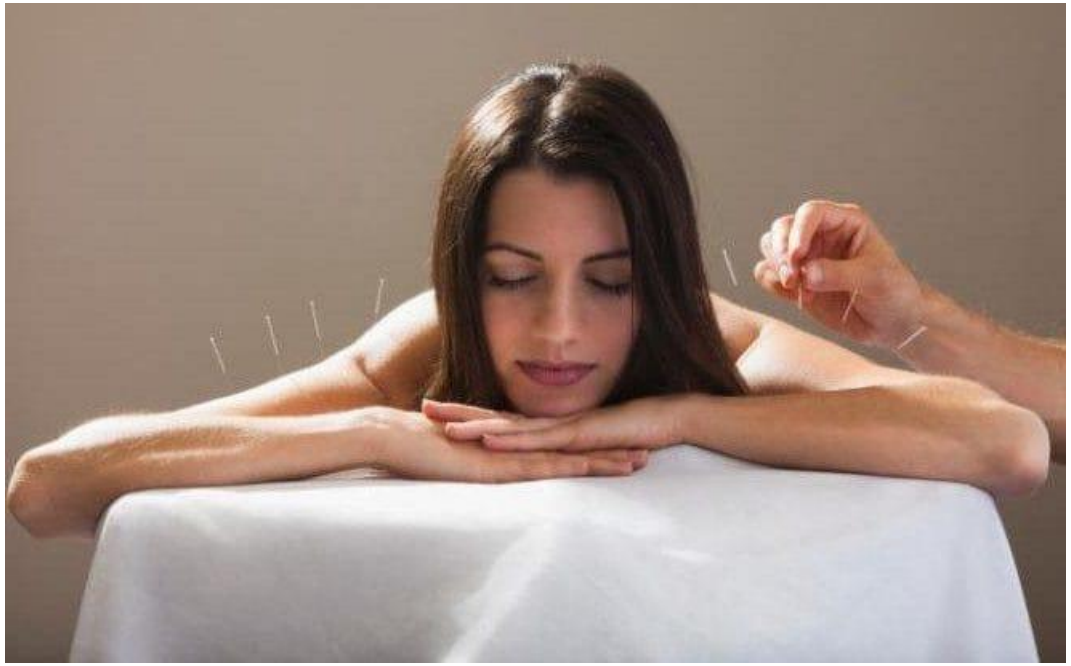
(3) Natural conception.

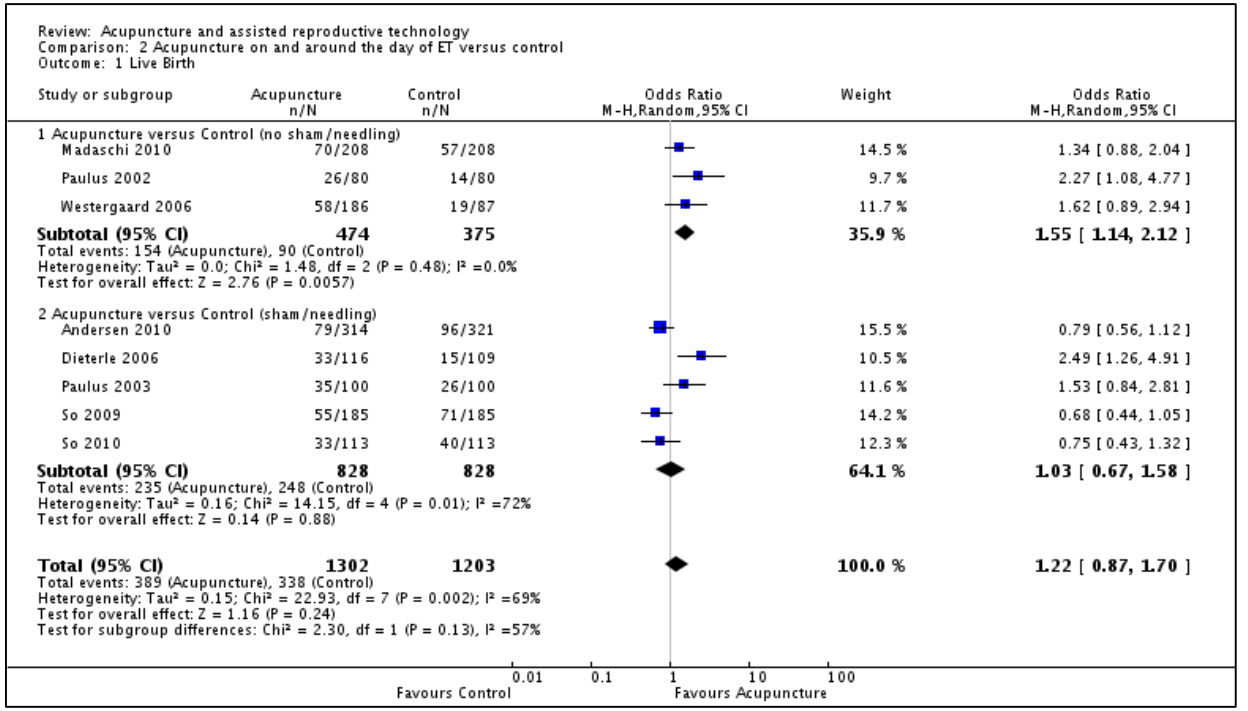
(4) This study reported 3 sets of twins in the combined antioxidants group and nil in the control group. Each twin birth was counted as one live birth event. IVF.

Cochrane Database of Systematic Reviews Dec 2014

repromed
Fertility excellence with heart

What about acupuncture?





Cochrane Database July 2013

- Meta-analyses have not demonstrated a statistical improvement in LBR or CPR with use of acupuncture anytime during the IVF cycle.

repromed
Fertility excellence with heart

Case 1 - Sadie

- Educate about normal natural fertility
- Check “lifestyle” factors and optimise where possible
- Offer to investigate if not pregnant by 6 months of trying

repromed
Fertility excellence with heart

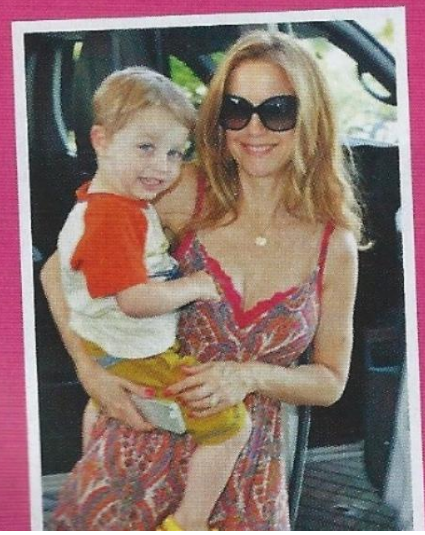
Case 2

- 47 year old Sharon is seeing you for her routine cervical smear when she says….. “I’ve been trying to have another child…what are my chances?”

Even though the chance of

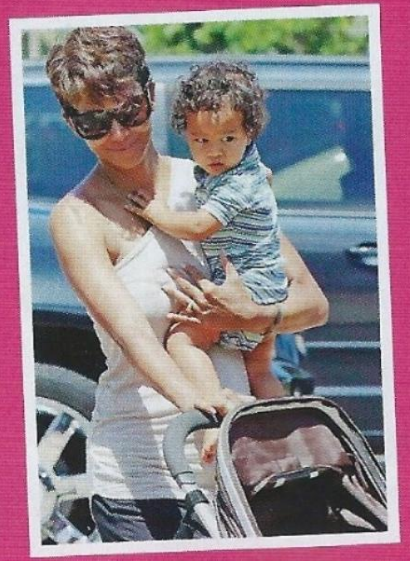
PROOF THAT IT'S NEVER TOO LATE

KELLY PRESTON
After the tragic death of her teenage son Jett, John Travolta's wife gave birth to their baby boy Benjamin, now three, at the age of 48.

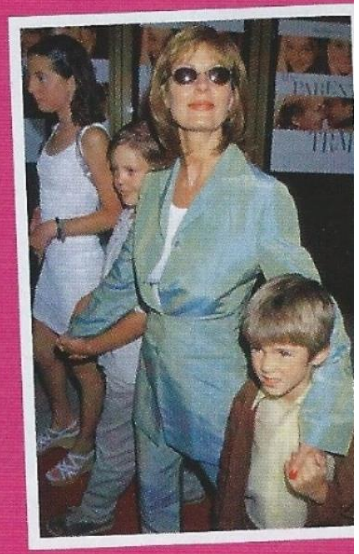


GEENA DAVIS
The *Thelma & Louise* actress isn't one to follow the rules – she was 48 when she welcomed twin sons Kian and Kaiis in 2004.

HALLE BERRY
Last year, the star was 47 when she gave birth to hubby Olivier Martinez's little boy Maceo, who turned one this month.



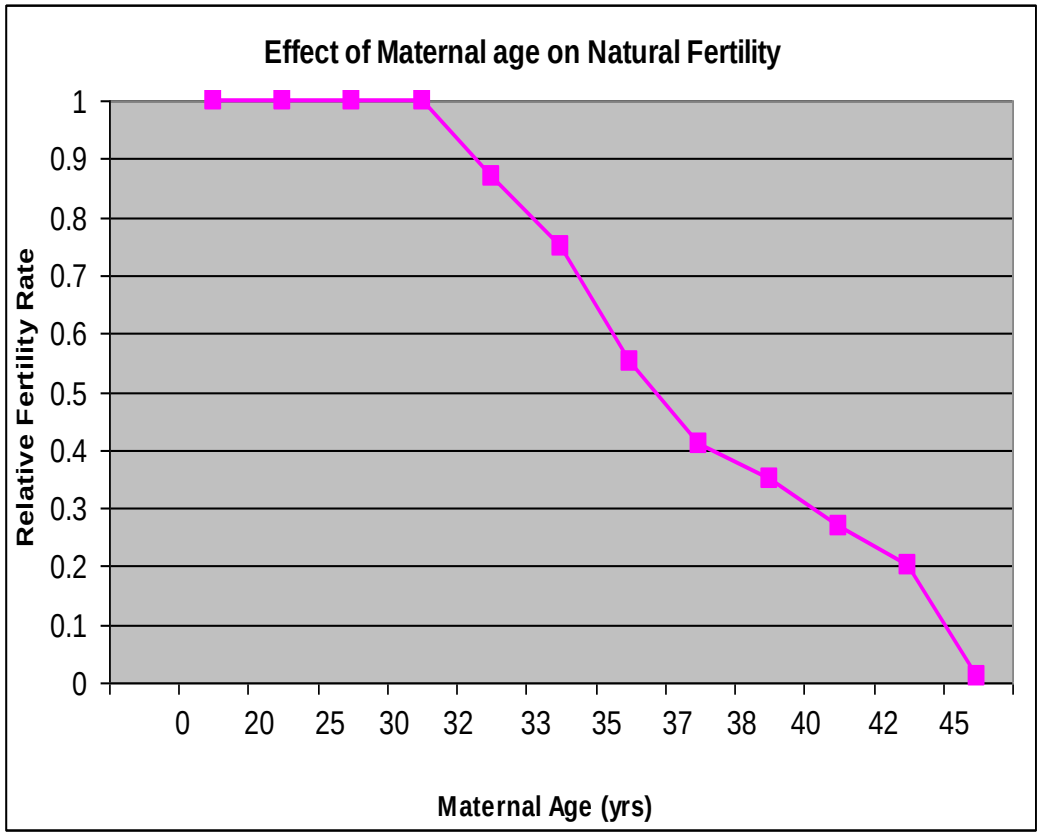
SUSAN SARANDON
The *Stepmom* actress and her then-husband Tim Robbins celebrated the arrival of son Miles in 1992, when she was 45.



Woman's Day, October 2014

repromed
Fertility excellence with heart

Female Age and Fertility – Natural Conception



- Few spontaneous LB's in women >43 years
- Oldest woman to conceive spontaneously 57 years
- Women who conceive at or over 45 years mostly grand multiparas
- Decline in fertility is multifactorial

reproMED
Fertility excellence with heart

Female Age and Fertility: Natural Conception

The “Hutterite Experiment”,
n=209

Age	Infertility Rate
25 years	3.5%
30 years	7%
35 years	11%
40 years	33%
41 years	50%
45 years	87%
49 years	100%

Tietze, C Fertility and Sterility 1957

reproMED
Fertility excellence with heart

Female Age and Fertility – does IVF help?

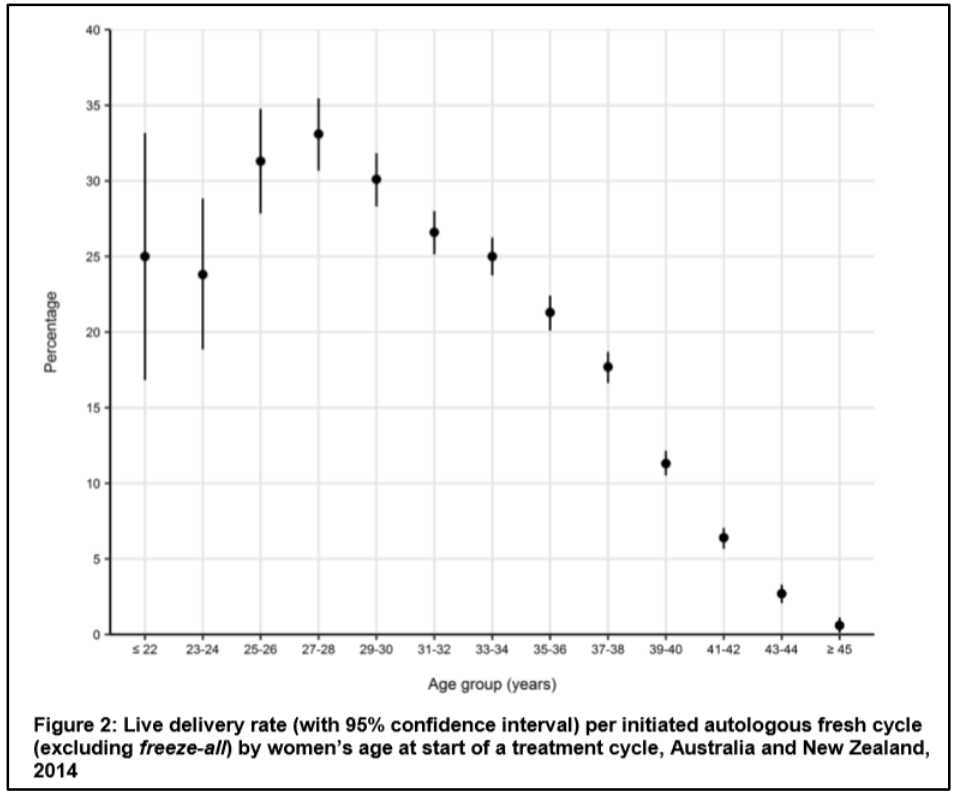


Figure 2: Live delivery rate (with 95% confidence interval) per initiated autologous fresh cycle (excluding *freeze-all*) by women's age at start of a treatment cycle, Australia and New Zealand, 2014

- Live Birth Rate/IVF cycle initiated
  - <30 years → 31.7%
  - 30-34 years → 26%
  - 35-39 years → 17.8%
  - 40-44 years → 6.6%
  - >45 years → 0.6%

ANZARD data 2014

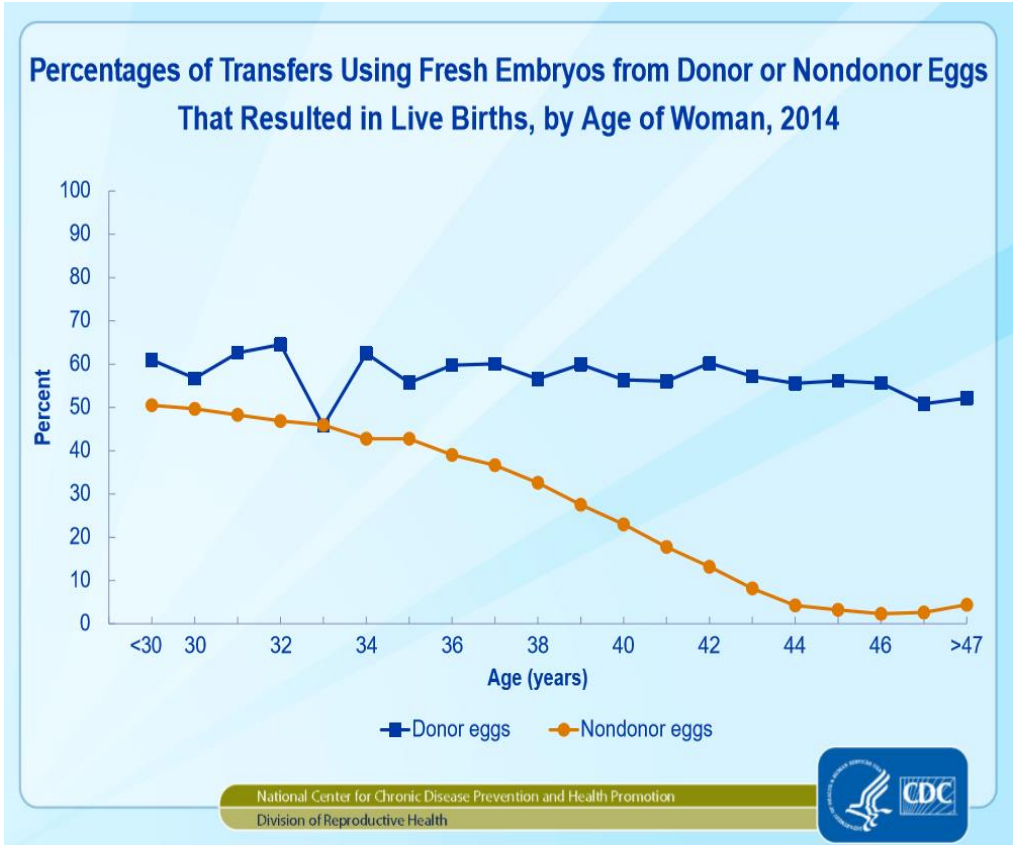
repromed
Fertility excellence with heart

Female Age and Fertility – Donor Egg Conception

- Live birth rate 18.3% in women >45 years using donor eggs

  ANZARD data 2014

- Live birth rates in US clinics vary from ~50-60% using donor eggs
  - Younger donors
  - >1 embryo transferred



CDC ART National Summary Report 2014

repromed
Fertility excellence with heart

Donor Egg ART can help but should we?

Childless woman, 66, world to give birth to t treatment

German primary school teacher, 65, gives birth to quadruplets two and a half months prematurely - and all babies have a 'good chance of surviving'

her reveals she is dying

Text Size A A A 4 Comments

repromed
Fertility excellence with heart

Treatment of older women….should we?

repromed
Fertility excellence with heart

Treatment of older women….should we?

Pro's

- High success rates with donor egg treatment
- Most women >45-50 years of age have good pregnancy outcomes and are able to cope with the physical and emotional stresses of pregnancy and parenting
- Emotional/financial stability

Treatment of older women….should we?

Pro's

- High success rates with donor egg treatment
- Most women >45-50 years of age have good pregnancy outcomes and are able to cope with the physical and emotional stresses of pregnancy and parenting
- Emotional/financial stability

Con's

- ↑ risk of gestational hypertension with donor egg pregnancies
- ↑ risk of other pregnancy complications, especially if multiple pregnancy
- ↑ maternal mortality/morbidity
- Possibility of parental death or serious illness while child is young
- Possibility that child will become a caregiver to aging parents
- Intergenerational issues

Case 2 - Sharon

- Advise chances of pregnancy unlikely unless with fertility treatments like donor egg
- Refer to Fertility clinic if wishes to discuss treatment,
  - Most clinics will not treat women >51 years
  - Not eligible for public funding if >40 years

repromed
Fertility excellence with heart

Case 3

- 34 year old Ashita comes to see you…..she and her husband have male factor infertility and have been told they need IVF. Ashita is worried though over a recent article in the NZ Herald……

New study finds babies born through IVF more likely to develop cancerous cells

1:00 PM Thursday Apr 27, 2017

Health | Health & Wellbeing | Parenting | ...

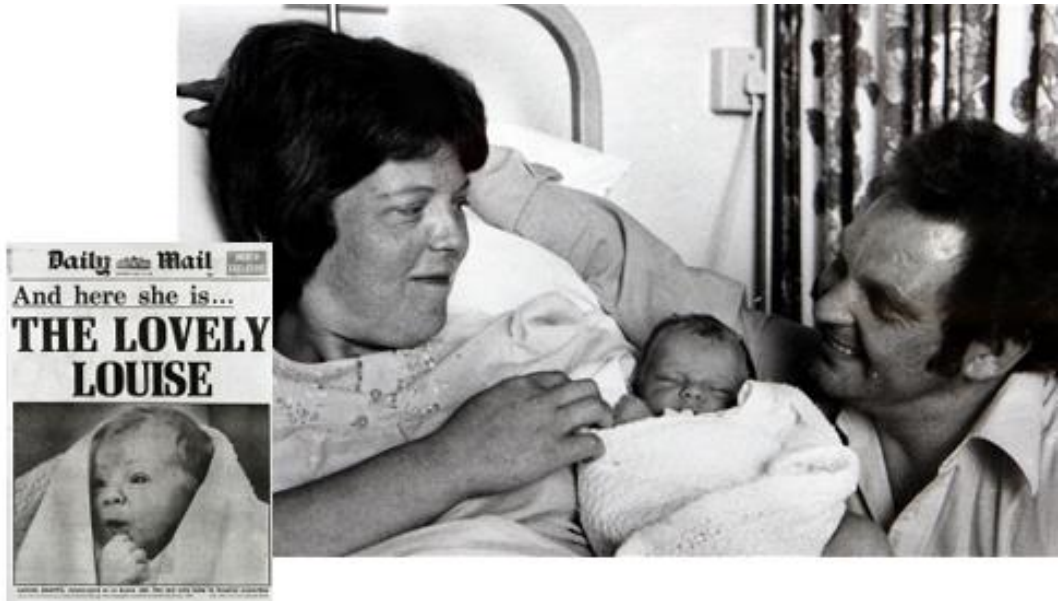
SHARE:

A new study has found babies born via IVF carry a higher risk of developing cancerous cells. Photo / 123RF

Millions of women around the world are turning to IVF to fall pregnant, but a new study has found these "test tube" babies are more likely to develop cancer later in life.

From 1991 until 2013, researchers from Israel's Ben-Gurion University of the

Pregnancy Outcomes after ART



- First birth after IVF 1978
- >5 million pregnancies achieved through ART since
- Outcomes among ART offspring up to 28 years of age have been reported, and are generally reassuring

Pregnancy Outcomes after ART

- ↑ risk of
  - Congenital anomalies
  - Preeclampsia
  - Preterm delivery
  - Low birth weight

- Most of these risks are due to multiple pregnancy but even singleton pregnancies have increased risks compared with spontaneous conceptions.

- Neurodevelopmental outcomes of children conceived by ART appear to be normal compared to matched controls.

reprOmed
Fertility excellence with heart

Pregnancy Outcomes after ART

- ↑ risk of cancer in offspring conceived through ART (RR 1.42; 95% CI 1.02-1.98)
  - Esp leukaemia's, neuroblastomas and retinoblastomas
  - Absolute risk is very small

Hargreave et al, Fertility and Sterility 2013

- ↑ risk of congenital abnormalities in offspring conceived through IVF (OR 1.37; 95% CI1.26-1.48)
  - All major organ systems; highest for the nervous system
  - Absolute risk is very small

Wen et al, Fertility and Sterility 2012

- Many postulated reasons but subfertility itself appears to have an adverse effect on pregnancy outcome, independent of its treatment

Case 4

- Lucy and Ben have a history of anovulatory infertility and recurrent implantation failure

Case 4

- 34 year old Lucy
  - >3 year history of anovulatory infertility due to PCOS

Case 4

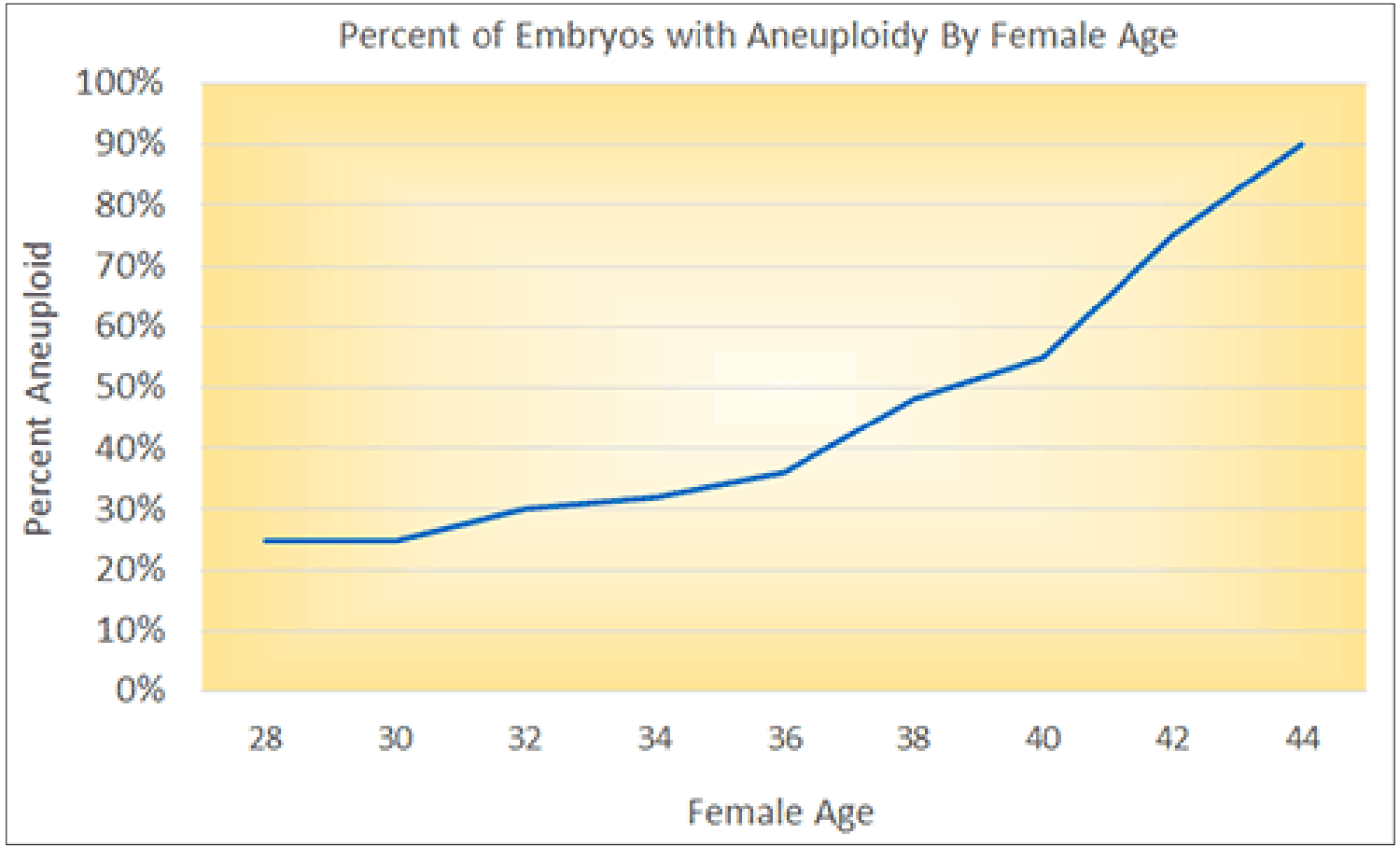
- 34 year old Lucy
  - >3 year history of anovulatory infertility due to PCOS
  - March 2013 IVF cycle
    - 30 eggs retrieved, 15 blastocysts frozen
    - May 2013-March 2014 underwent 9 frozen embryo replacements before conceiving

Case 4

- 34 year old Lucy
  - >3 year history of anovulatory infertility due to PCOS
  - March 2013 IVF cycle
    - 30 eggs retrieved, 15 blastocysts frozen
    - May 2013-March 2014 underwent 9 frozen embryo replacements before conceiving
  - Jan 2017 IVF cycle with EmbryoSelect
    - 16 eggs retrieved, 5 blastocysts created and biopsied, 1 euploid embryo

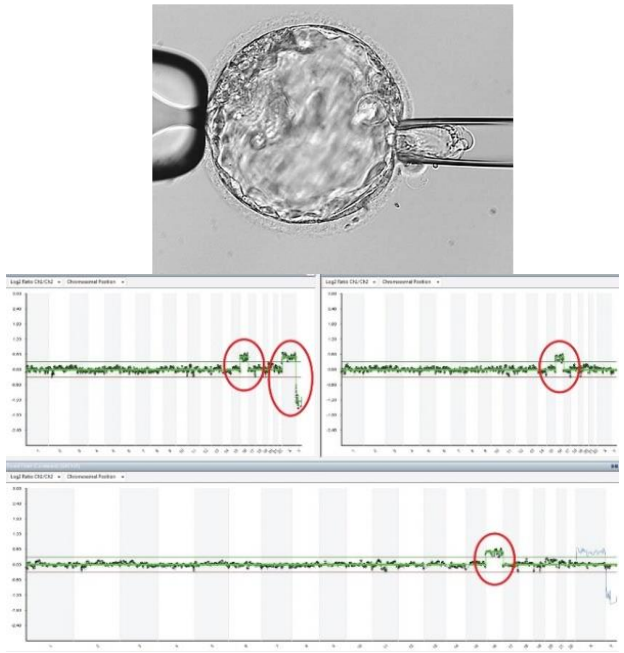
Case 4

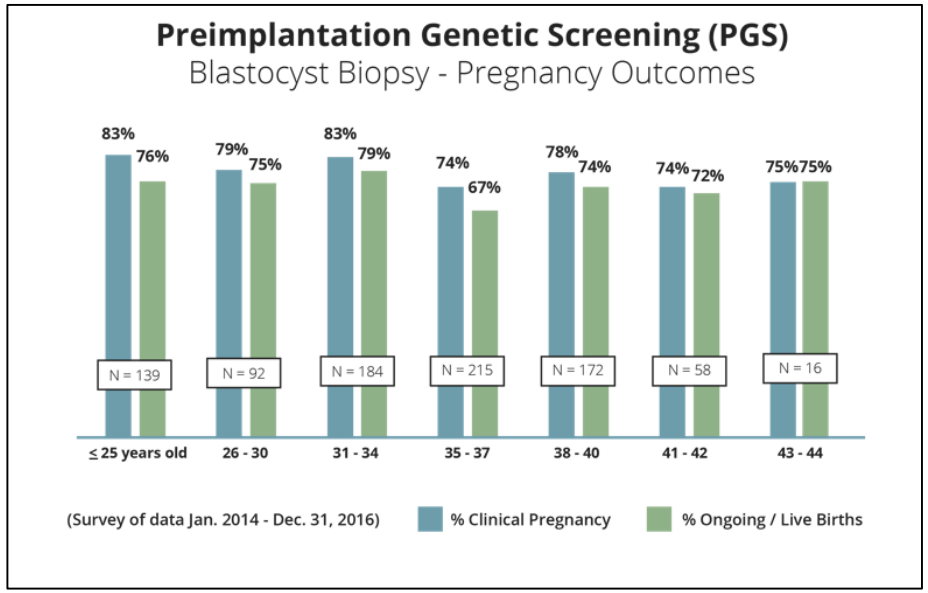
- 34 year old Lucy
  - >3 year history of anovulatory infertility due to PCOS
  - March 2013 IVF cycle
    - 30 eggs retrieved, 15 blastocysts frozen
    - May 2013-March 2014 underwent 9 frozen embryo replacements before conceiving
  - Jan 2017 IVF cycle with EmbryoSelect
    - 16 eggs retrieved, 5 blastocysts created and biopsied, 1 euploid embryo
  - Mar 2017 – euploid embryo transferred → currently pregnant



- 40-60% of preimplantation embryos are aneuploid (commonest reason for the relatively low implantation rate of both natural and assisted conceptions)

Preimplantation Genetic Screening

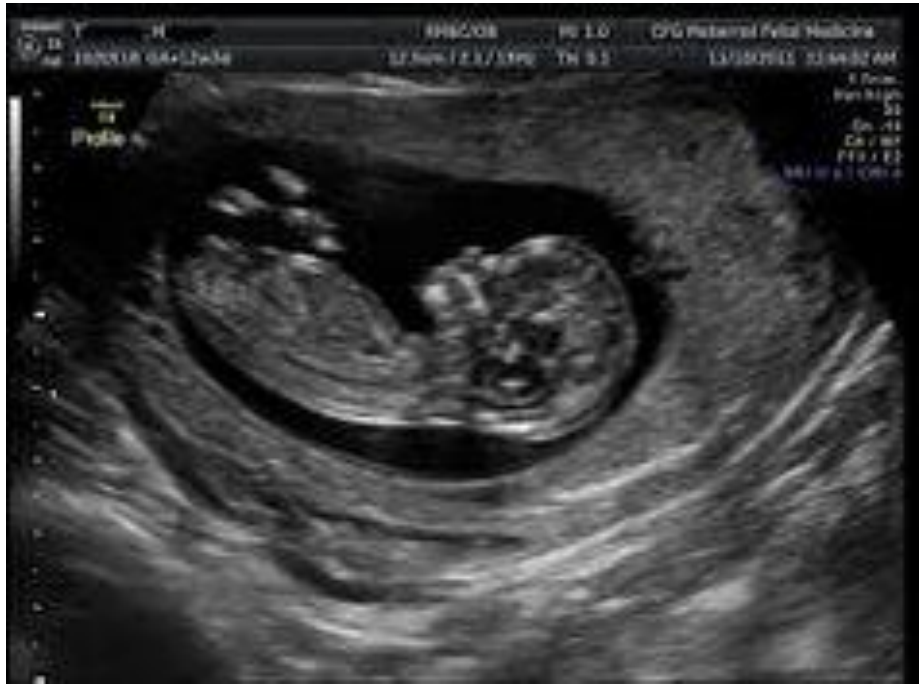




- Similar process to PGD but screens all the chromosomal pairs instead of looking for a single gene disorder or sex-chromosome linked condition
- ↑ LBR if can replace a euploid embryo (no matter what the maternal age)
- Most appropriate for couples with RIF, RPL, advanced maternal age

reproMED
Fertility excellence with heart

Case 4 – Lucy and Ben



repromed
Fertility excellence with heart

repromed

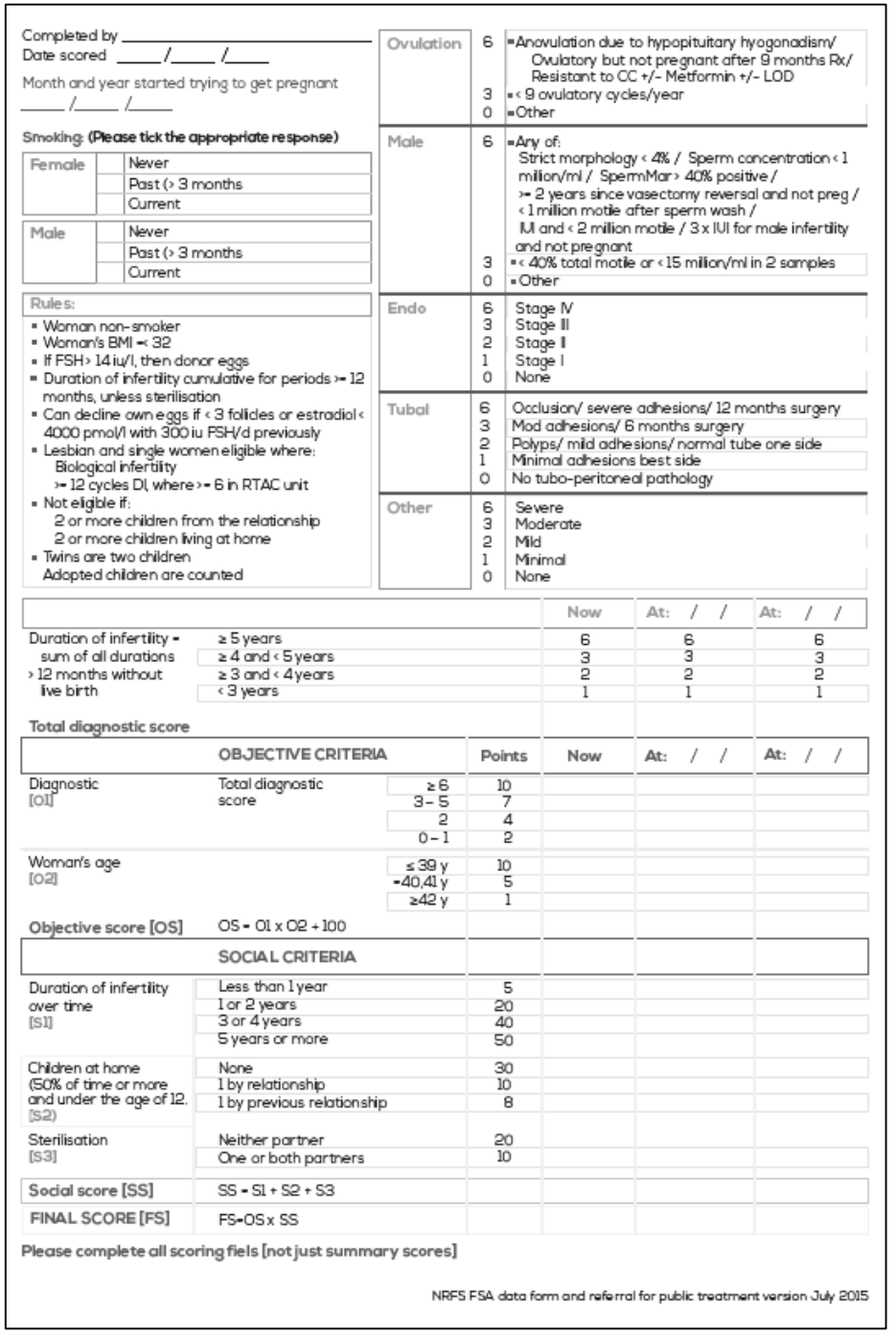
Fertility excellence with heart

Thank You

karen.buckingham@repromed.co.nz

CPAC Scoring for Publicly Funded Fertility Treatment

- CPAC threshold still 65 points
- Exclusion criteria:
  - Female age ≥40 years
  - Female BMI >32
  - Current smoker
- Up to two “packages of care” available (1 “package” could be 4 x IUI cycles or 1 x IVF cycle)
- Current wait time ~12 months for IVF treatment



Completed by _____
Date scored ____/____/____
Month and year started trying to get pregnant ____/____/____

Smoking: **(Please tick the appropriate response)**

Female		Never
		Past (> 3 months
		Current
Male		Never
		Past (> 3 months
		Current

Rules:
- Woman non-smoker
- Woman's BMI =< 32
- If FSH> 14 iu/l, then donor eggs
- Duration of infertility cumulative for periods >= 12 months, unless sterilisation
- Can decline own eggs if < 3 follicles or estradiol < 4000 pmol/l with 300 iu FSH/d previously
- Lesbian and single women eligible where:
  Biological infertility
  >= 12 cycles DI, where >= 6 in RTAC unit
- Not eligible if:
  2 or more children from the relationship
  2 or more children living at home
- Twins are two children
  Adopted children are counted

Ovulation	6	=Anovulation due to hypopituitary hyogonadism/ Ovulatory but not pregnant after 9 months Rx/ Resistant to CC +/- Metformin +/- LOD
	3	=< 9 ovulatory cycles/year
	0	=Other
Male	6	=Any of: Strict morphology < 4% / Sperm concentration < 1 milion/ml / SpermMar> 40% positive / >= 2 years since vasectomy reversal and not preg / < 1 million motile after sperm wash / IUI and < 2 million motile / 3 x IUI for male infertility and not pregnant
	3	=< 40% total motile or < 15 milion/ml in 2 samples
	0	=Other
Endo	6	Stage IV
	3	Stage III
	2	Stage II
	1	Stage I
	0	None
Tubal	6	Occlusion/ severe adhesions/ 12 months surgery
	3	Mod adhesions/ 6 months surgery
	2	Polyps/ mild adhesions/ normal tube one side
	1	Minimal adhesions best side
	0	No tubo-peritoneal pathology
Other	6	Severe
	3	Moderate
	2	Mild
	1	Minimal
	0	None

		Now	At: / /	At: / /
Duration of infertility = sum of all durations > 12 months without live birth	≥ 5 years	6	6	6
	≥ 4 and < 5 years	3	3	3
	≥ 3 and < 4 years	2	2	2
	< 3 years	1	1	1

Total diagnostic score

	OBJECTIVE CRITERIA		Points	Now	At: / /	At: / /
Diagnostic [O1]	Total diagnostic score	≥ 6	10			
		3 – 5	7			
		2	4			
		0 – 1	2			
Woman's age [O2]		≤ 39 y	10			
		=40,41 y	5			
		≥42 y	1			
Objective score [OS]	OS = O1 x O2 + 100					
	SOCIAL CRITERIA					
Duration of infertility over time [S1]	Less than 1 year		5			
	1 or 2 years		20			
	3 or 4 years		40			
	5 years or more		50			
Children at home (50% of time or more and under the age of 12. [S2]	None		30			
	1 by relationship		10			
	1 by previous relationship		8			
Sterilisation [S3]	Neither partner		20			
	One or both partners		10			
Social score [SS]	SS = S1 + S2 + S3					
FINAL SCORE [FS]	FS=OS x SS					

Please complete all scoring fiels [not just summary scores]

NRFS FSA data form and referral for public treatment version July 2015

CPAC Scoring

Completed by _____
Date scored ____/____/____

Month and year started trying to get pregnant
____/____/____

Smoking: **(Please tick the appropriate response)**

Female		Never
		Past (> 3 months
		Current
Male		Never
		Past (> 3 months
		Current

Rules:

- Woman non-smoker
- Woman's BMI =< 32
- If FSH > 14 iu/l, then donor eggs
- Duration of infertility cumulative for periods >= 12 months, unless sterilisation
- Can decline own eggs if < 3 follicles or estradiol < 4000 pmol/l with 300 iu FSH/d previously
- Lesbian and single women eligible where:
  Biological infertility
  >= 12 cycles DI, where >= 6 in RTAC unit
- Not eligible if:
  2 or more children from the relationship
  2 or more children living at home
- Twins are two children
  Adopted children are counted

Ovulation	6	=Anovulation due to hypopituitary hyogonadism/ Ovulatory but not pregnant after 9 months Rx/ Resistant to CC +/- Metformin +/- LOD
	3	=< 9 ovulatory cycles/year
	0	=Other
Male	6	=Any of: Strict morphology < 4% / Sperm concentration < 1 milion/ml / SpermMar > 40% positive / >= 2 years since vasectomy reversal and not preg / < 1 million motile after sperm wash / IUI and < 2 million motile / 3 x IUI for male infertility and not pregnant
	3	=< 40% total motile or < 15 milion/ml in 2 samples
	0	=Other
Endo	6	Stage IV
	3	Stage III
	2	Stage II
	1	Stage I
	0	None
Tubal	6	Occlusion/ severe adhesions/ 12 months surgery
	3	Mod adhesions/ 6 months surgery
	2	Polyps/ mild adhesions/ normal tube one side
	1	Minimal adhesions best side
	0	No tubo-peritoneal pathology
Other	6	Severe
	3	Moderate
	2	Mild
	1	Minimal
	0	None

		Now	At: / /	At: / /
Duration of infertility = sum of all durations > 12 months without live birth	≥ 5 years	6	6	6
	≥ 4 and < 5 years	3	3	3
	≥ 3 and < 4 years	2	2	2
	< 3 years	1	1	1
Total diagnostic score				

	OBJECTIVE CRITERIA		Points	Now	At: / /	At: / /
Diagnostic [O1]	Total diagnostic score	≥ 6	10			
		3 – 5	7			
		2	4			
		0 – 1	2			
Woman's age [O2]		≤ 39 y	10			
		=40,41 y	5			
		≥42 y	1			
Objective score [OS]	OS = O1 x O2 + 100					
	SOCIAL CRITERIA					
Duration of infertility over time [S1]	Less than 1 year		5			
	1 or 2 years		20			
	3 or 4 years		40			
	5 years or more		50			
Children at home (50% of time or more and under the age of 12. [S2]	None		30			
	1 by relationship		10			
	1 by previous relationship		8			
Sterilisation [S3]	Neither partner		20			
	One or both partners		10			
Social score [SS]	SS = S1 + S2 + S3					
FINAL SCORE [FS]	FS=OS x SS					

Please complete all scoring fiels [not just summary scores]

NRFS FSA data form and referral for public treatment version July 2015

reproMED
Fertility excellence with heart

Cost of Private Fertility Treatment

• Ovulation induction with CC/Letrozole	$340/cycle
• Intrauterine insemination	$1595/cycle
• Lipiodol flushing	$500-1000
• In vitro fertilization	$10,000-12,000/cycle
• Embryo Select	$3,400
• Frozen embryo replacement	$1810/cycle

reproMED
Fertility excellence with heart