

Effectiveness of treatments for subfertility: a comparative review

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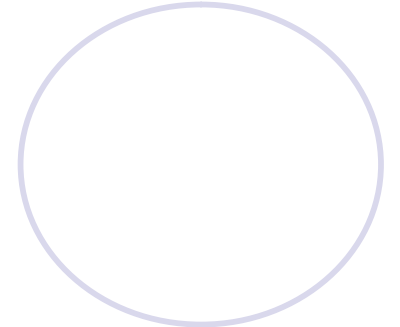
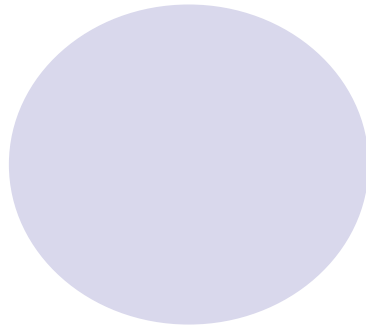
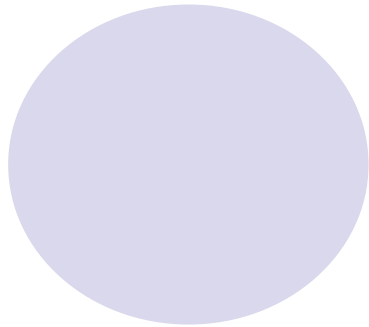
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Outline

- Subfertility is a chronic health condition.
- The key outcome is a healthy singleton birth.
- Evaluation of outcomes of treatment requires cohort analysis.
- Studies must account for population characteristics.
- NaProTechnology performs well for relevant outcomes, in comparison to ART.
- Research is ongoing in NaProTechnology.

Subfertility is a chronic health condition.



Subfertility



- Subfertility is a syndrome, not a diagnosis.
- It is a relative, not absolute condition.
 - Among a group of couples that have not conceived for a period of time, there is still a probability of conception (with or without treatment).



There is wide variability among couples
with respect to capacity to conceive

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Causes of subfertility



- There are many possible causes.
- Usually, more than one abnormality or cause is present.
- Subfertility is a couple's problem, not a woman's problem.
- Causes of subfertility are not usually single events, but accumulate over time.

Determining causes of subfertility

- Wide variation in diagnostic evaluation
 - Unfortunate trend towards minimal evaluation!
- Issue of cause versus association of some diagnostic abnormalities
 - Comparison to normally fertile couples necessary.

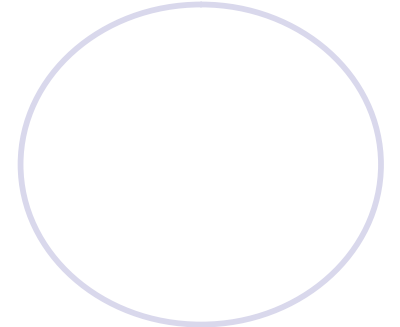
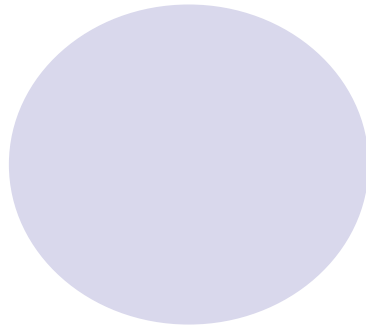
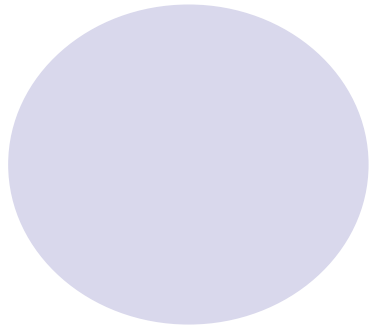


Lifetime prevalence

- U.K. survey 6584 women ages 40-54
 - 16% consulted doctor to try to conceive
 - 8% received treatment
 - 4% at least one pregnancy from treatment
 - 4.3% never had live birth

Oakley, Doyle, Maconochie, *Hum Reprod* 2008

The key outcome is a healthy singleton birth.

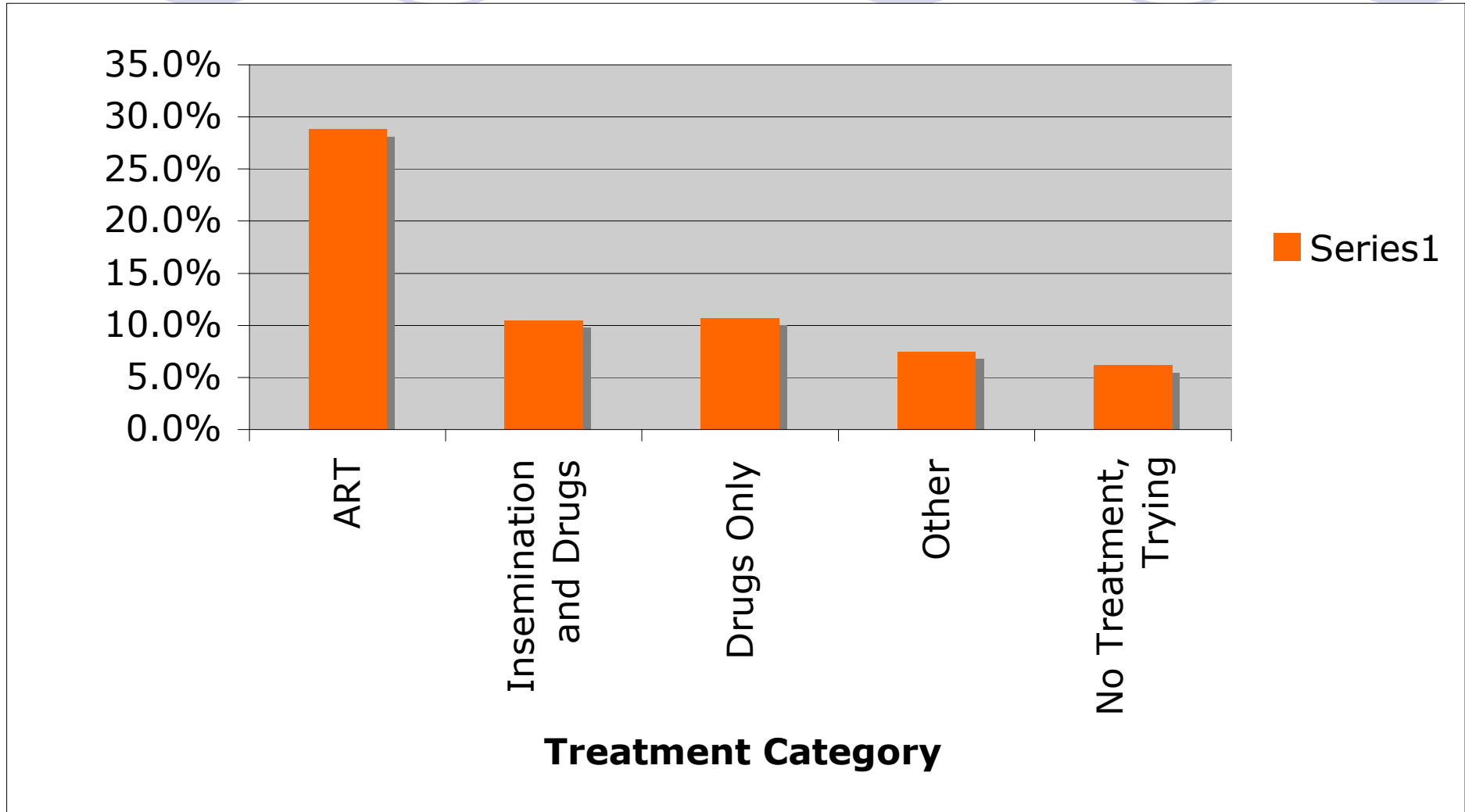


Possible outcomes



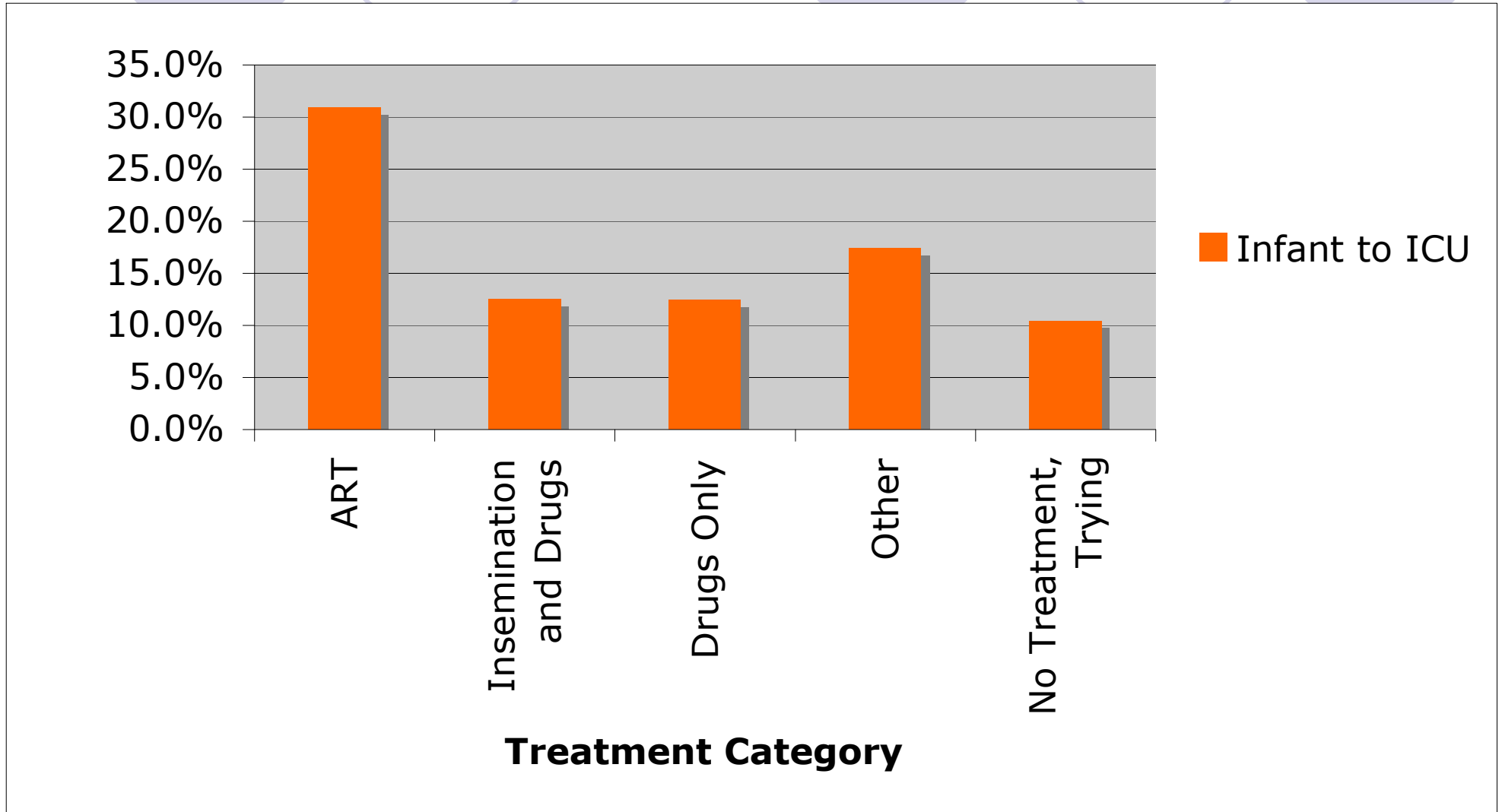
- Pregnancy: “chemical” or “clinical”
- *Live birth*
- Single or multiple gestation
- Prematurity
- Neonatal and childhood morbidity

Subfertility treatment and low birth weight



Stanford, Ellis-Simonsen, Baksh, 2004-5 PRAMS data

Subfertility treatment and NICU admission



Stanford, Ellis-Simonsen, Baksh, 20004-5 PRAMS data

Adverse outcomes associated with ART

- *independent* of multiple gestation (meta-analysis)

- Low birth weight [OR 1.8]
- Very low birth weight [OR 2.7]
- Prematurity [OR 2.0]
- Perinatal mortality [OR 2.2]

Jackson and Croughan; *Obstet Gynecol* 2004

Potential adverse outcomes of ART

- Birth defects

- Population-based registry Australia

- 1993-7

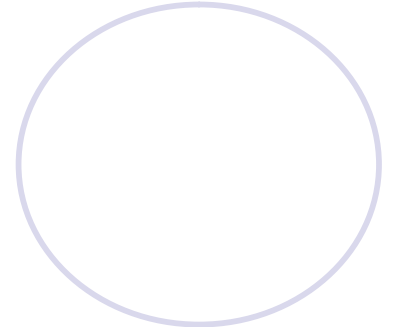
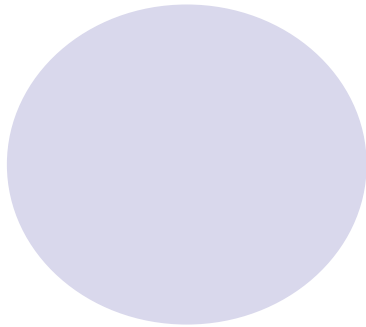
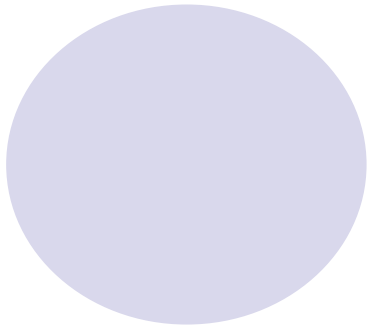
- IVF 9.0%

- ICSI 8.6%

- Natural conception 4.2%

Hansen et al, *NEJM* 2002

Evaluation of outcomes of
treatment requires cohort
analysis.



Ways to measure outcomes



- Per cycle rates

- Misleading

- “Acute condition” approach

- ignores experience over time

- Cohort

- Appropriate comparison of different treatments

- “Chronic condition” approach

- Able to look at big picture

Cycle versus cohort analyses

	IUI	IUI + superov	IVF
N	86	85	87
Per cycle	7.4%	8.7%	12.2%

Goverede et al, *Lancet* 2000

Cycle versus cohort analyses

	IUI	IUI + superov	IVF
N	86	85	87
Per cycle	7.4%	8.7%	12.2%
6 month cumulative	31%	37%	38%

Goverede et al, *Lancet* 2000

U.S. National Registry of ART Clinics

- All data in terms of treatment cycles
 - Unknown number of women, cycles per woman, or centers per woman
- 74,957 cycles with fresh non-donor eggs
 - 64,280 retrievals, 60,299 transfers, 23,042 pregnancies, 19,042 live births
 - 38% pregnancy per transfer
 - 25% live birth per cycle of treatment

ART cohort



- 1315 couples in the Netherlands
- Up to 5 cycles of IVF +/- ICSI
- Cumulative probability of *pregnancy*
 - Crude rate 42.4
 - Life table 64.7
- Mean woman's age 32.8 years
- Mean time trying: 3.6 years
- First ART treatment- no previous attempts

Very few randomized trials of ART

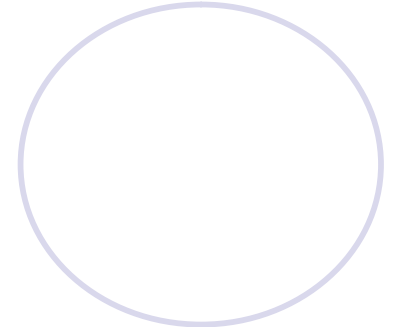
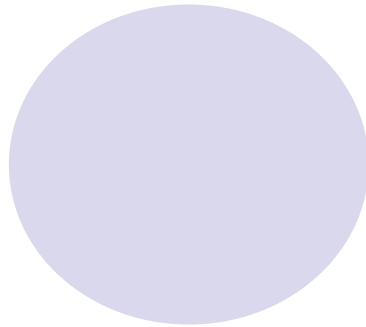
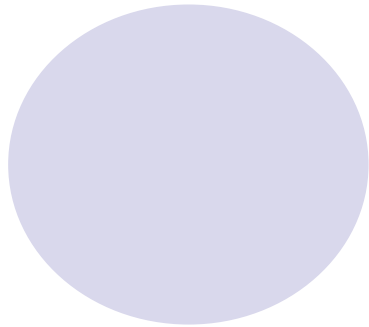
- For unexplained infertility
 - No difference between 1 cycle IVF and 6 months no treatment (1 small trial)
 - No difference between IVF and IUI (1 trial)
 - “The effectiveness of IVF relative to other treatment options for unexplained infertility remains unproven. Adverse events and the costs associated with the interventions compared have not been adequately assessed. ”

- Pandian Z, Bhattacharya S, Nikolaou D, Vale L, Templeton A.. In vitro fertilisation for unexplained subfertility (Cochrane Review). In: *The Cochrane Library* , Issue 4, 2003.

Subfertility is a chronic condition.

An informative evaluation of treatment, and comparisons of treatment, must be done on a cohort basis.

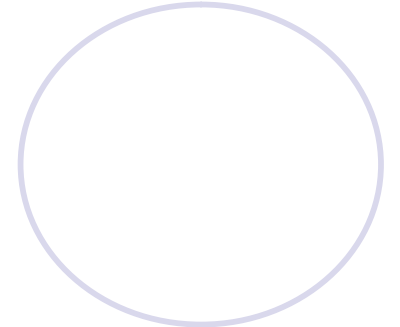
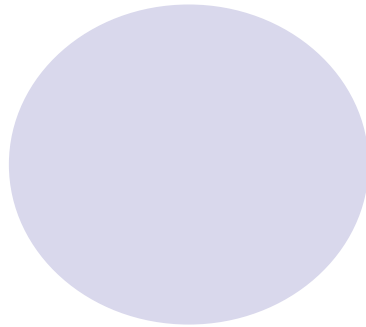
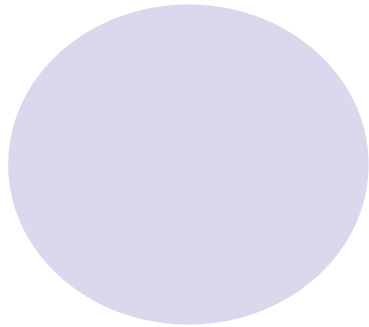
**Studies must account for
population characteristics.**



Strong predictors of pregnancy or birth rates

- Woman's age
- Length of time trying
- Diagnoses (some)
- Prior pregnancy or birth
- Prior treatment attempts

NaProTechnology performs well
for the relevant outcomes, in
comparison to ART.





Galway study- NaProTechnology

- 1239 couples seen 1998-2002
- 1072 trying for at least one year and started treatment
 - Average female age 35.8 yrs
 - Average time trying to conceive 5.6 yrs
 - 33% with history of unsuccessful IVF
 - 24% prior birth

Stanford, Parnell, Boyle. J Amer Board Family Medicine, *in press*

Characteristics by conception status

	All	Conceived	Did not conceive
Total number	1072	364	708
Woman's age	35.8	34.8	36.4
Mean (range)	(25-48)	(25-45)	(26-48)
Prior years attempting	5.6	4.8	6.1
Mean (range)	(1-20)	(1-17)	(1-20)
Had previous live birth	24%	30%	20%
Received previous ART	33%	21%	39%

Stanford, Parnell, Boyle. JABFM, *in press*

Galway NaPro study



- Couples followed until live birth, completion of 2 years' treatment, or drop out from treatment.
- Crude live birth rates: all who start treatment in denominator
- Adjusted live birth rates: adjust for drop-out by life table analysis

Galway NaPro study- live birth rates

- All couples
- Crude rate: 25.5
- Adjusted rate: 52.8

Galway NaPro study- live birth rates

Woman's age	Number couples	Crude live birth rate	Adjusted live birth rate
<=30 yrs	86	33.7	59.1
>30 to 35 yrs	412	32.5	58.6
>35 to 40 yrs	423	21.0	46.1
> 40 yrs	151	13.9	50.9

Stanford, Parnell, Boyle. JABFM, *in press*

Galway NaPro study- live birth rates

Prior time attempting	Number couples	Crude live birth rate	Adjusted live birth rate
1-3 yrs	246	36.6	66.0
>3 to 6 yrs	468	27.6	55.4
>6 to 9 yrs	210	18.6	44.9
> 9 yrs	118	11.9	42.8

Stanford, Parnell, Boyle. JABFM, *in press*

Galway NaPro study- live birth rates

Prior ART attempts	Number couples	Crude live birth rate	Adjusted live birth rate
0	702	30.8	61.5
1	128	22.7	41.9
2	125	14.4	34.9
3 or more	97	10.3	19.8

Stanford, Parnell, Boyle. JABFM, *in press*

Galway NaPro study- live birth rates

Prior births	Number couples	Crude live birth rate	Adjusted live birth rate
None	257	35.8	73.9
1 or more	785	23.1	48.5

Stanford, Parnell, Boyle. JABFM, *in press*

Galway NaPro study- birth outcomes

Outcome	Number births	Percentage
Twins	13	4.5
<37 weeks	15	5.2
<2500 grams	13	4.5
<1500 grams	4	1.4

Stanford, Parnell, Boyle. JABFM, *in press*

Galway Study- predicting live birth

Characteristic	Odds ratio	Lower 95% C.I.	Upper 95% C.I.
Women's age	0.91	0.87	0.95
Years trying	0.92	0.86	0.98
Prior pregnancy	2.7	1.9	3.9
Prior IVF	0.84	0.56	1.2

Galway Study- predicting live birth

Characteristic	Odds ratio	Lower 95% C.I.	Upper 95% C.I.
Low luteal prog. alone	0.12	0.06	0.24
Low luteal estrogen alone	0.24	0.10	0.58
Low luteal estrogen & prog	12.0	4.5	31.8
Limited mucus	2.3	1.6	3.3
Male factor	0.5	0.30	0.82

The image features five light purple circles of varying sizes and styles. Two are solid, one is a thin outline, and two are semi-transparent. They are arranged in a loose pattern around the central text.

**Research is ongoing in
NaProTechnology.**



International NaProTechnology
Evaluation and Surveillance of
Treatment for subfertility and
Miscarriage

iNEST



iNEST Primary Objectives

- Document live birth rates in couples treated with NaProTechnology for subfertility or miscarriage.
- Investigate how live birth rates relate to couple characteristics
- Clarify how live birth rates vary with different evaluation or treatment strategies
 - initial versus delayed surgical evaluation



iNEST Design

- Prospective cohort
 - Couples based
- NPT practice-based initiation
- Patient follow-up *independent* of practice
- Follow all couples *regardless of treatment continuation or discontinuation*
- Obtain treatment data from NPT physician



iNEST Progress

- Jean Golden-Tevald, Morningstar Family Health Care, New Jersey, began enrolling patients Feb. 2006
- Joseph Stanford, University of Utah, began enrolling patients July 2007



More iNEST practices

- Practices with IRB approval already in place
 - Boyle, Galway, Ireland
 - Tham, Toronto, Canada
 - Carpentier, Massachusetts, USA
- Practices very close
 - Parker, Ohio, USA
 - Rota, Perth, Australia
 - Stegman, Pennsylvania, USA

Participating patients

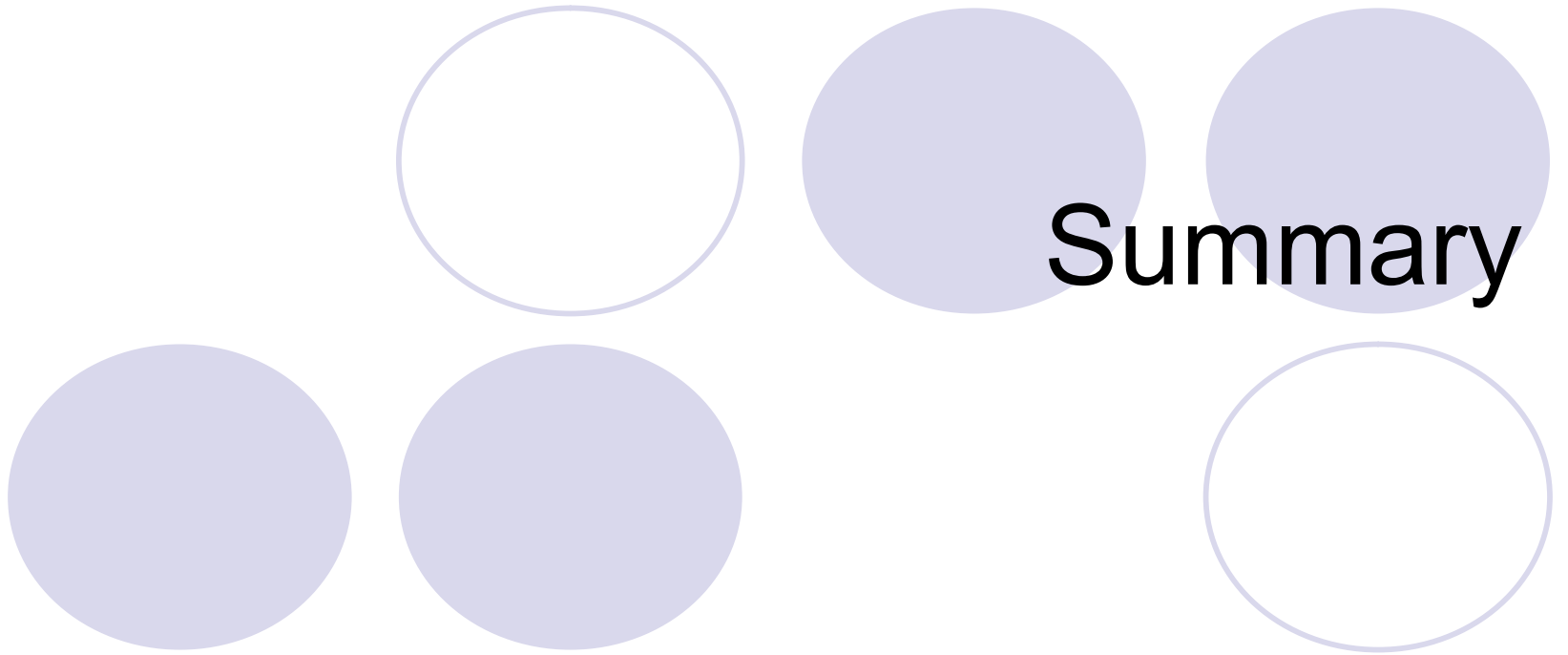


- The whole process is relatively “transparent” to the patient.
- Care received is not dependent on participation.
- Written informed consent is obtained for 3-year follow-up with option for more.



Main Outcome

- Live birth up to 3 years after beginning NPT
- Examine in terms of baseline characteristics and treatment choices





Take home points

Subfertility is a chronic health condition, and should be treated accordingly.

The most relevant treatment outcome for couples and for public health is singleton live birth with a healthy infant and child.

Evaluation of subfertility treatment should be done on a cohort basis, not per-cycle.



Take home points

Comparisons between studies need to account for differences in study populations, especially woman's age, length of time previously attempting conception, prior pregnancy or birth, prior treatment attempts, and underlying diagnoses.

The limited comparative data suggest that NaProTechnology meets or exceeds the relevant outcomes in comparison to other fertility therapies.



Take home points

Ongoing research will allow us to offer much more detailed information to couples about their specific prognosis with treatment with NaProTechnology.