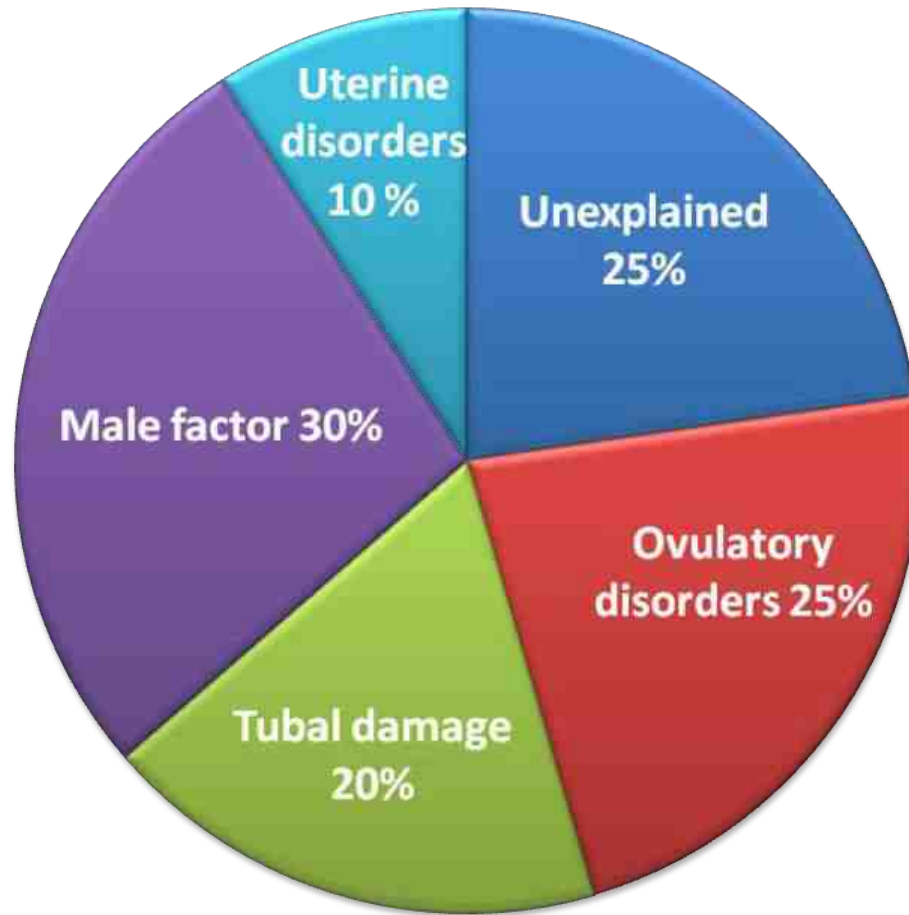


Unexplained infertility: What should be the first-line treatment?

Roy Homburg

Tel Aviv, Israel,
Homerton Fertility Centre, London
& Liverpool Womens Hospital, UK



The place of IVF

IVF/ICSI should be offered as **primary** treatment of infertility when:

- Mechanical infertility
- Severe male infertility
- Oocyte donation
- Surrogacy
- PGD

The place of IVF

IVF should **NOT** be offered as **primary** treatment for:

- Hypogonadotrophic-hypogonadism
- Anovulation, PCOS
- Mild/moderate sperm problem
- Unexplained infertility ???

The place of IVF

- “IVF should be offered as first line therapy to all infertile couples regardless of the type of infertility”

Gleicher & Karande, 2001

Treatment for a boil on the finger



.....or amputation of the arm?



Unexplained (Idiopathic) Infertility

- Lack of a diagnosis.
- 1-3 years of regular, unprotected intercourse –
 - tests for
ovulation
 - tubal patency
 - semen analysis
 - all normal.

People are having less sex than they were in the 1990s

■ Men ■ Women

Average number of times per month



Source: National Survey of Sexual Attitudes and Lifestyles

Unexplained Infertility

When to intervene?

- >35 years old – 1 year
- <35 years old, with children - 2 years

Unexplained Infertility

- Up to 30% of all couples presenting with infertility after 1 year.
- No intervention for 3 years -
33-60% will conceive.

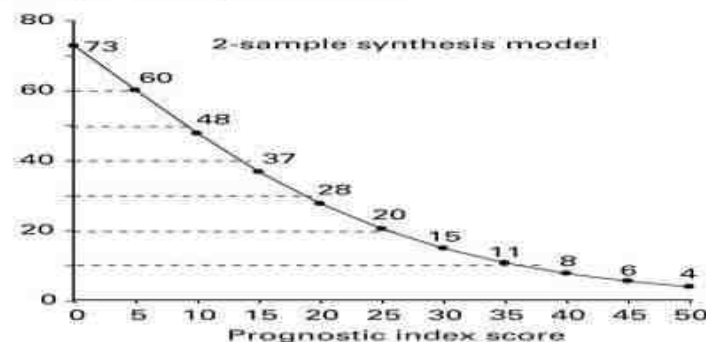
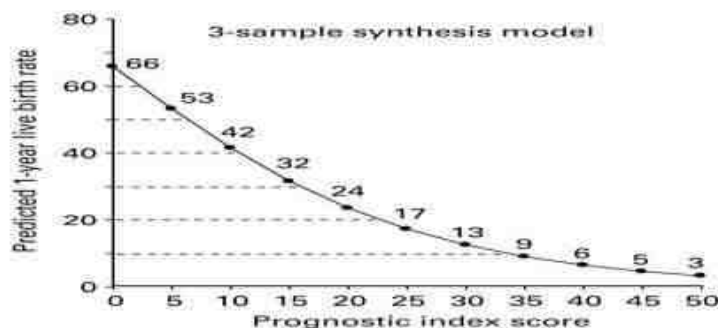
Selection of patients

- Good prognosis - < 2 years infertility
 - < 35 years old
 - previous pregnancy
- Poorer prognosis when - >3 years infertility
 - > 35 years old
- >40 years old often diagnosed as unexplained but mostly reduced ovarian reserve.

Score chart of the 3-sample and 2-sample synthesis models to estimate the chance of spontaneous pregnancy within 1 year after intake resulting in live birth.

							Score 3-sample	Score 2-sample
Woman's age (y)	21-25	26-31	32-35	36-37	38-39	40-41		
3-sample model	0	3	7	10	13	15	
2-sample model	0	2	6	9	11	12	
Duration of subfertility (y)	1	2	3-4	5-6	7-8			
3-sample model	0	3	7	12	18		
2-sample model	0	2	5	9	13		
Type of subfertility		Secondary	Primary					
3-sample model		0	8				
2-sample model		0	6				
Motility (%)	≥ 60	40-59	20-39	0-19				
3-sample model	0	2	4	6			
2-sample model	0	2	4	6			
Referral status	Secondary-care couple	Tertiary-care couple						
3-sample model	0	4					
2-sample model	0	4					
Post-Coital-Test	Normal	Abnormal						
2-sample model	0	14					
Prognostic Index Score (Sum)						

Procedure: circle the score for each of the variables, transfer to rightmost column and add to get the prognostic index score. Insert the score in the appropriate figure below in order to read off the chance of spontaneous pregnancy within 1 year resulting in live birth. (Example: according to the 3-sample synthesis model, a couple with a 28-year-old woman, with primary subfertility of 2 years duration, with 30% motile sperm, referred by a gynaecologist has a prognostic index score equivalent to $3 + 3 + 4 + 4 = 22$. This score corresponds to a cumulative 12-months spontaneous pregnancy rate of 21%.)



Hunault C et al. Hum. Reprod. 2004;19:2019-2026

Unfavourable prognosis

- unexplained infertility

- RCT n=116

	1 cycle IVF-eSET	3 cycles IUI-COH
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Ongoing pregnancies	24%	21%
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Custers et al, 2011

Unexplained – good prognosis

- < 2 years infertility, < 35 years old – similar chance of pregnancy with or without IUI or IVF!
(Steures et al, 2006; Brandes et al, 2011)

Good prognosis

- unexplained infertility

- n=544

Overtreatment (n=198) = started treatment within 6 months after finalizing work up

versus

Expectant treatment (n=346)

Kersten et al, 2015

Good prognosis

- unexplained infertility

Within 6 months

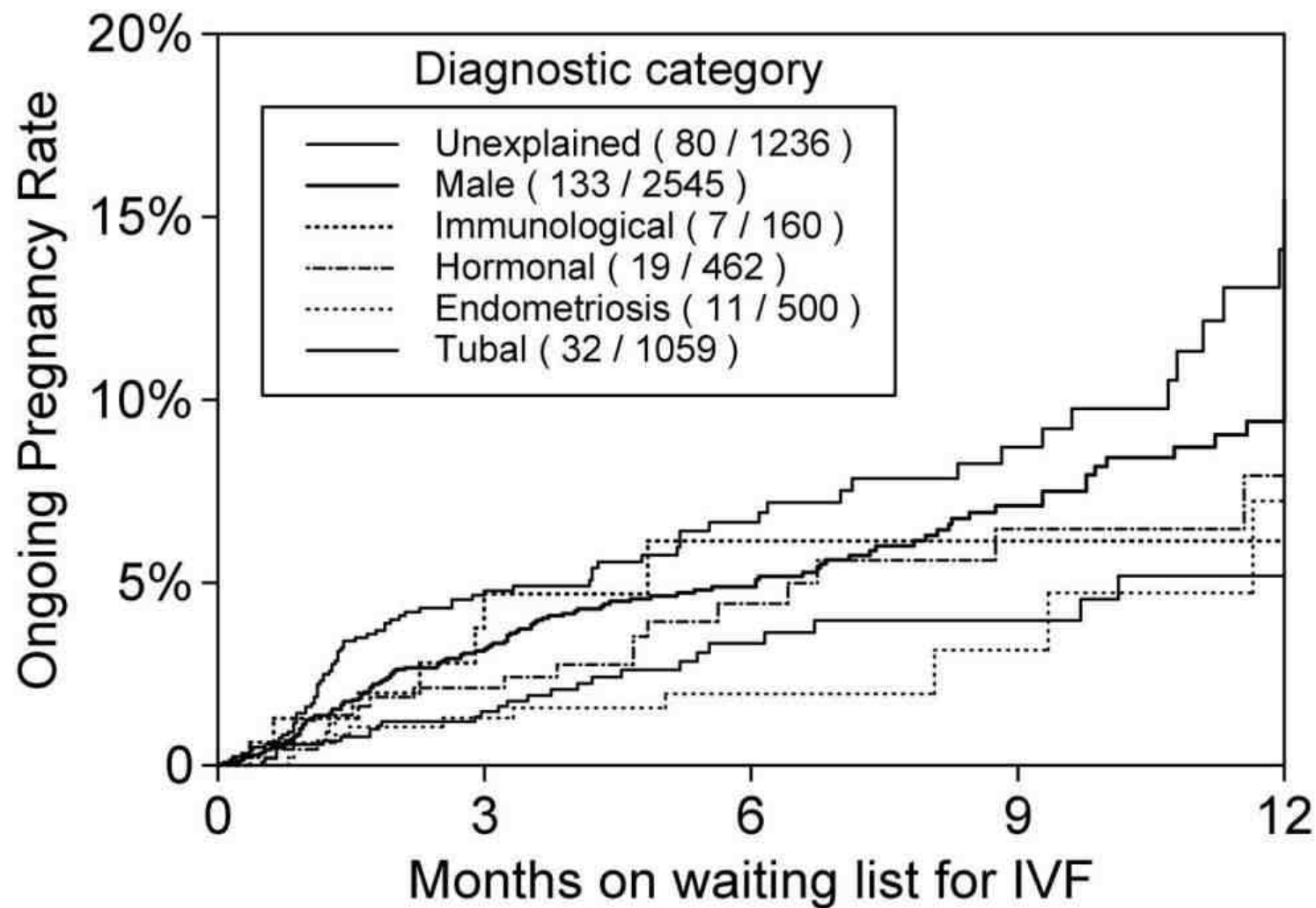
	<u>Over Rx</u>	<u>Expectant</u>
Pregnancy	35.4%	39%
Ongoing pregnancy	27.8%	31.2%

Within 1 year

Pregnancy	52.1%	50%
Ongoing pregnancy	42.4%	40.5%

Kersten et al, 2015

Cumulative chance of an ongoing treatment-free pregnancy, against time since registration on the waiting list for IVF or ICSI, separately for diagnostic categories.



Eijkemans M et al. Hum. Reprod. 2008;23:1627-1632

Treatment possibilities for Unexplained Infertility

- Expectant
- IUI
- Gonadotrophin stimulation
- Clomifene + IUI
- Gonadotrophins + IUI
- IVF/ICSI

Why use superovulation + IUI for unexplained infertility?

Superovulation

- May overcome subtle defect in ovulatory function.
- Increases number of eggs available for fertilisation.
- Increases estradiol levels.



Weapons of mass conception

Why use superovulation + IUI for unexplained infertility?

IUI

- Greater density of good motile sperm.
- Placed closer to oocyte.
- Good timing

Unexplained Infertility

IUI or IVF?

- Efficiency
- Multiple pregnancy rate
- Complications
- Drop outs
- Cost efficiency

Using RCT's & live birth rates

Complications and drop-outs

IVF vs IUI

IVF

- - more invasive
- - more complications
- - less compliance
- - higher cumulative drop-out rate
- - more expensive

compared to IUI

Multiple birth rates, IVF vs IUI

	<u>IVF</u>	<u>IUI</u>
Twins	21%	9.5%
Triplets	0.8%	1.0%
Total	21.8%	10.5%

IUI

- Live birth rate / couple
27.2% after a mean of 2.8 cycles

Khalil et al, 2001

- Cumulative clinical pregnancy rate
after 3 cycles – 27%

Nandi, Homburg et al, British Fertility Society Meeting, 2015

- IUI + 10 minutes bed-rest – 29% PR

Saleh et al, 2007

Cost efficiency

1 live birth

- IUI + ovarian stimulation \$ 5108
- IVF \$ 13,132



Goverde, 2000

HFEA Database 2011

2011	IVF/ICSI	Live birth rate	IUI	Pregnancy rate
Pregnancies	13,703		572	
Women	48,141	27.2 %		
Cycles	61,726 (\$6K each)	21.1%	4174 (\$1K each)	13.7%
Embryos	89.648	15.3%		

IVF for unexplained infertility.

Pandian, Bhattacharya, Vale & Templeton

IVF for unexplained infertility. Cochrane Database, 2005

- No difference in live-birth rates between IVF and IUI either with or without ovarian stimulation.

Updated in 2012

- No difference in live birth rates, IVF versus IUI + COS - OR 1.09 (0.74-1.59)

National Institute for Clinical Excellence (NICE) - 2012

- “Expectant treatment for up to 2 years
– then IVF”.
- No evidence whatsoever for this recommendation.



Online Survey on NICE Guidelines for Unexplained Infertility

Nandi, Homburg et al, Human Fertility, 2014

- 136 members of BFS responded to an e-mail questionnaire.
- Only 16% recommend IVF as 1st line treatment
- Only 27% would change their practice in accord with the new guidelines;
- 30% would definitely not change and the rest waiting for evidence.

IUI: a UK survey on adherence to NICE guidelines by fertility clinics

Kim D, Child T, Farquhar C. BMJ Open, 2015

- 46 fertility clinics in UK responded
(70% of all clinics licensed to provide IUI in UK)
- 96% continued to offer IUI despite NICE recommendations.
- 4 clinics reduced no. of IUI, 6 restricted indications.
- Lack of adherence to the recommendations!

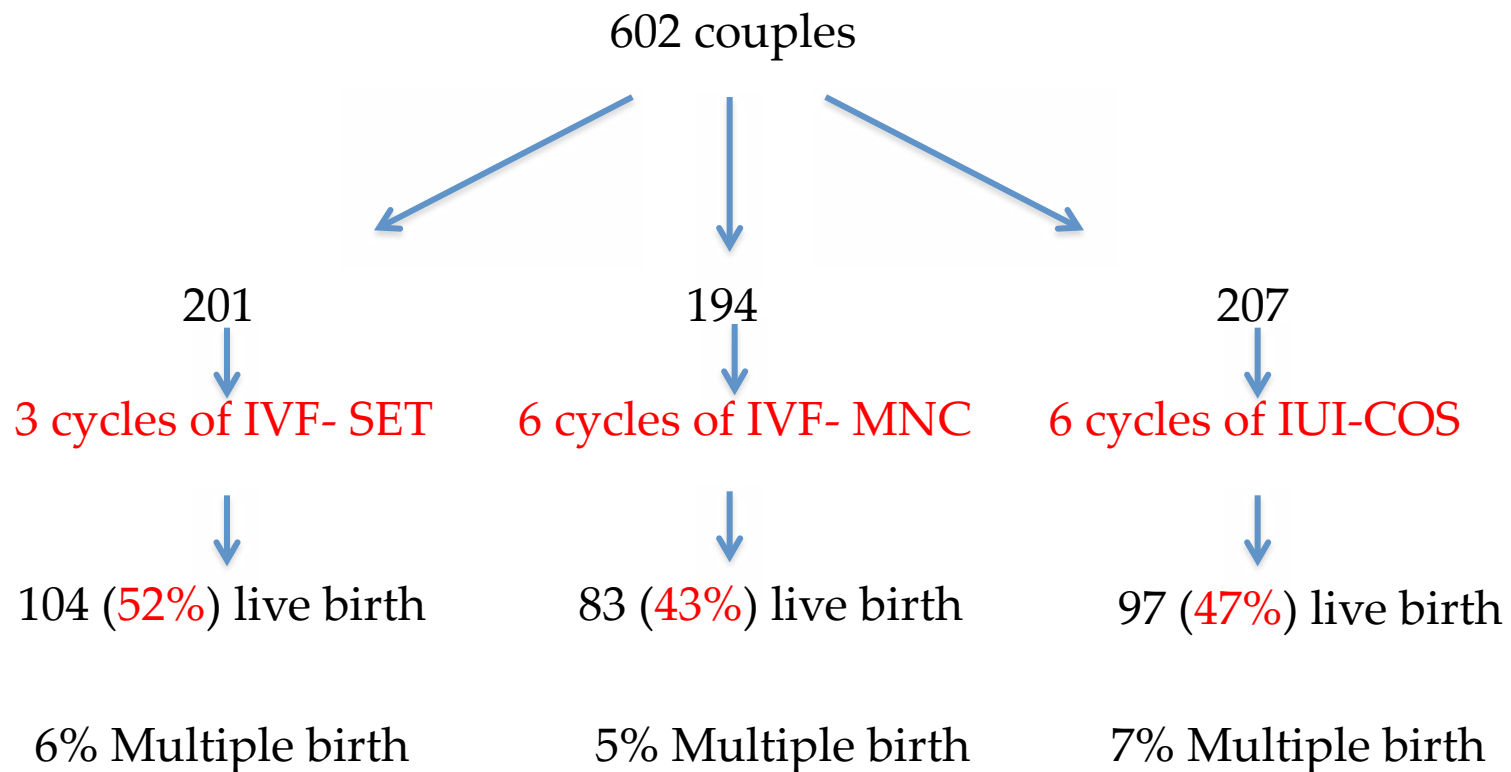
RESEARCH

Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation

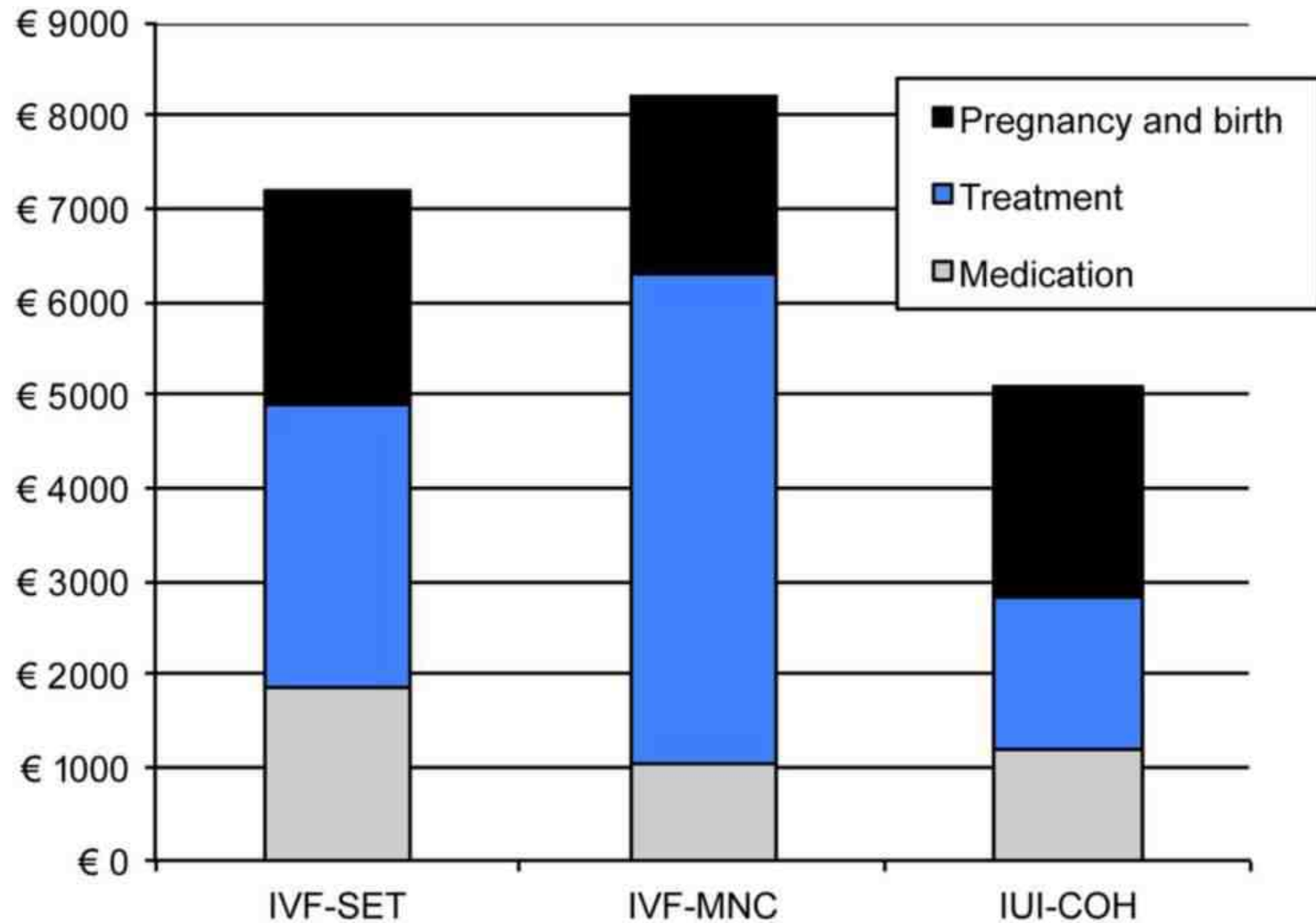
 OPEN ACCESS

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- Multicenter three arm, parallel group, randomised controlled non-inferiority trial involving 17 centres in the Netherlands
- Couples with at least 12 months of unexplained or mild male subfertility, with the female partner between 18 and 38 years, an unfavourable prognosis for natural conception.



Mean costs per couple.



R.I. Tjon-Kon-Fat et al. Hum. Reprod. 2015;humrep.dev193

Incremental cost-effectiveness ratios (ICER)

- IVF-SET compared with IUI-COH was
€43,375

reflecting the additional costs necessary to achieve one additional healthy child in the IVF-SET group, compared with IUI-COH.

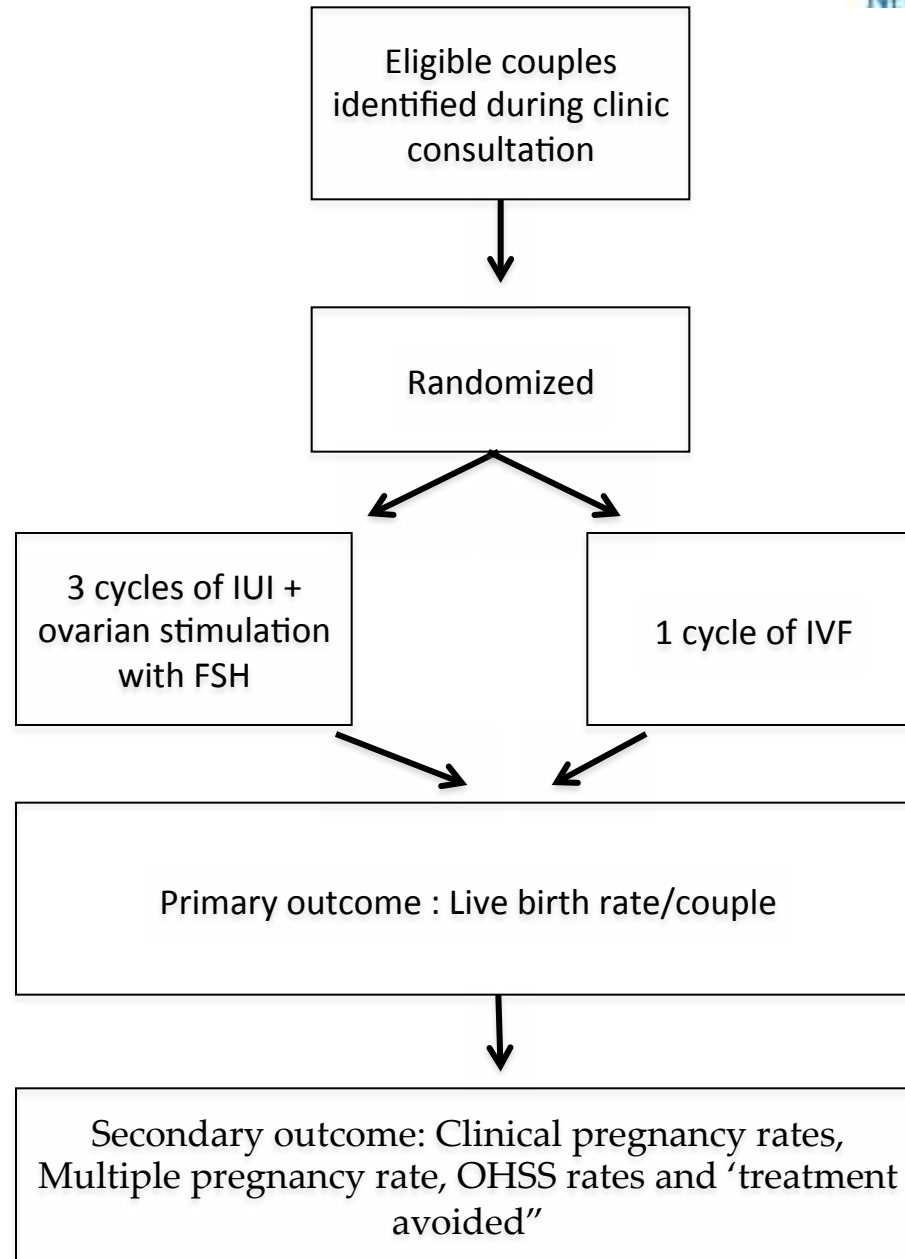
Tjon-Kon-Fat et al, Hum Reprod,

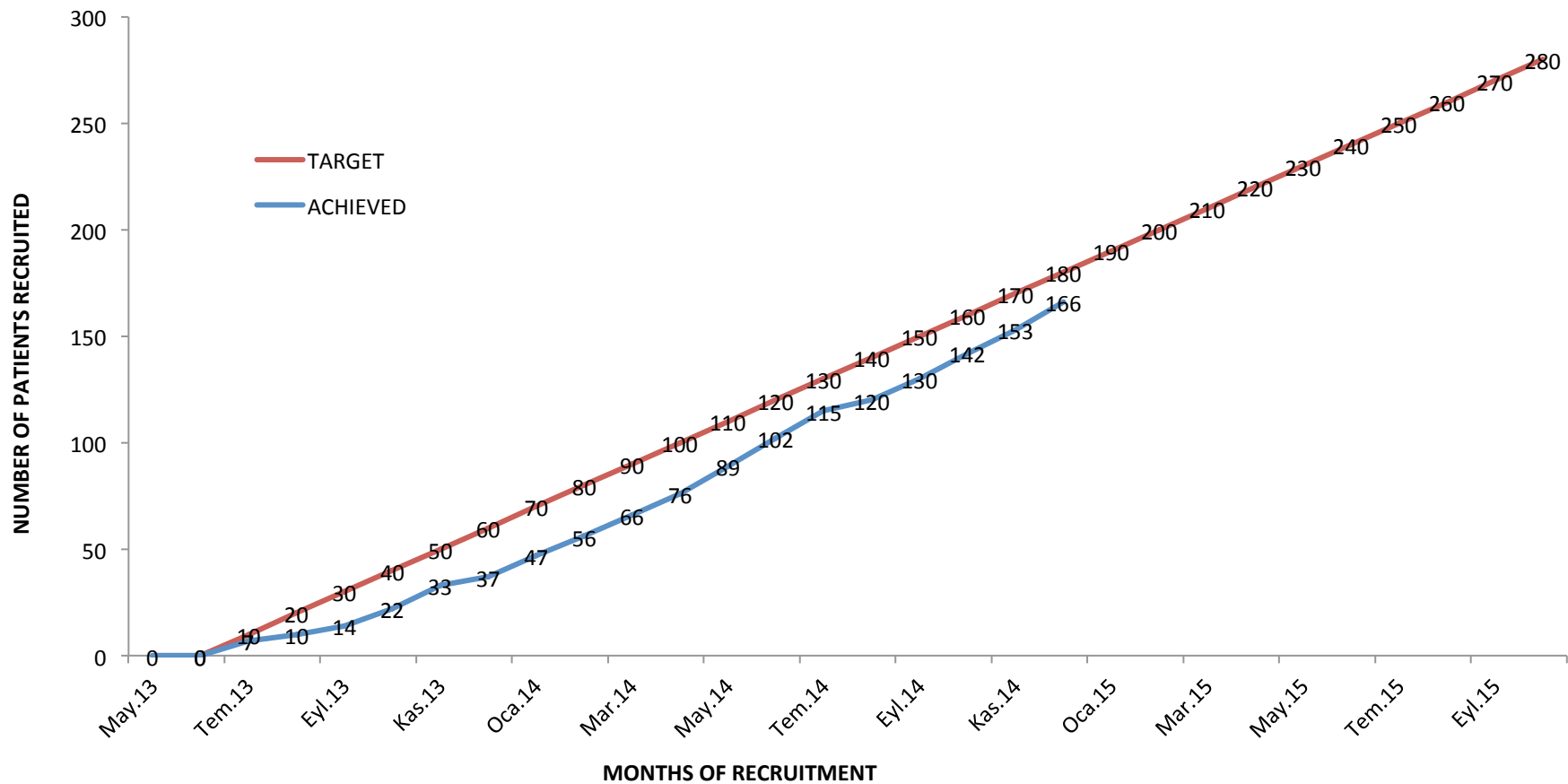
2015

Unexplained subfertility trial

- RCT – treatment naive couples
3 cycles IUI + COH
versus
1 cycle IVF/ICSI
- 280 couples to be recruited by September 2015

Nandi & Homburg, Homerton Fertility Centre, London



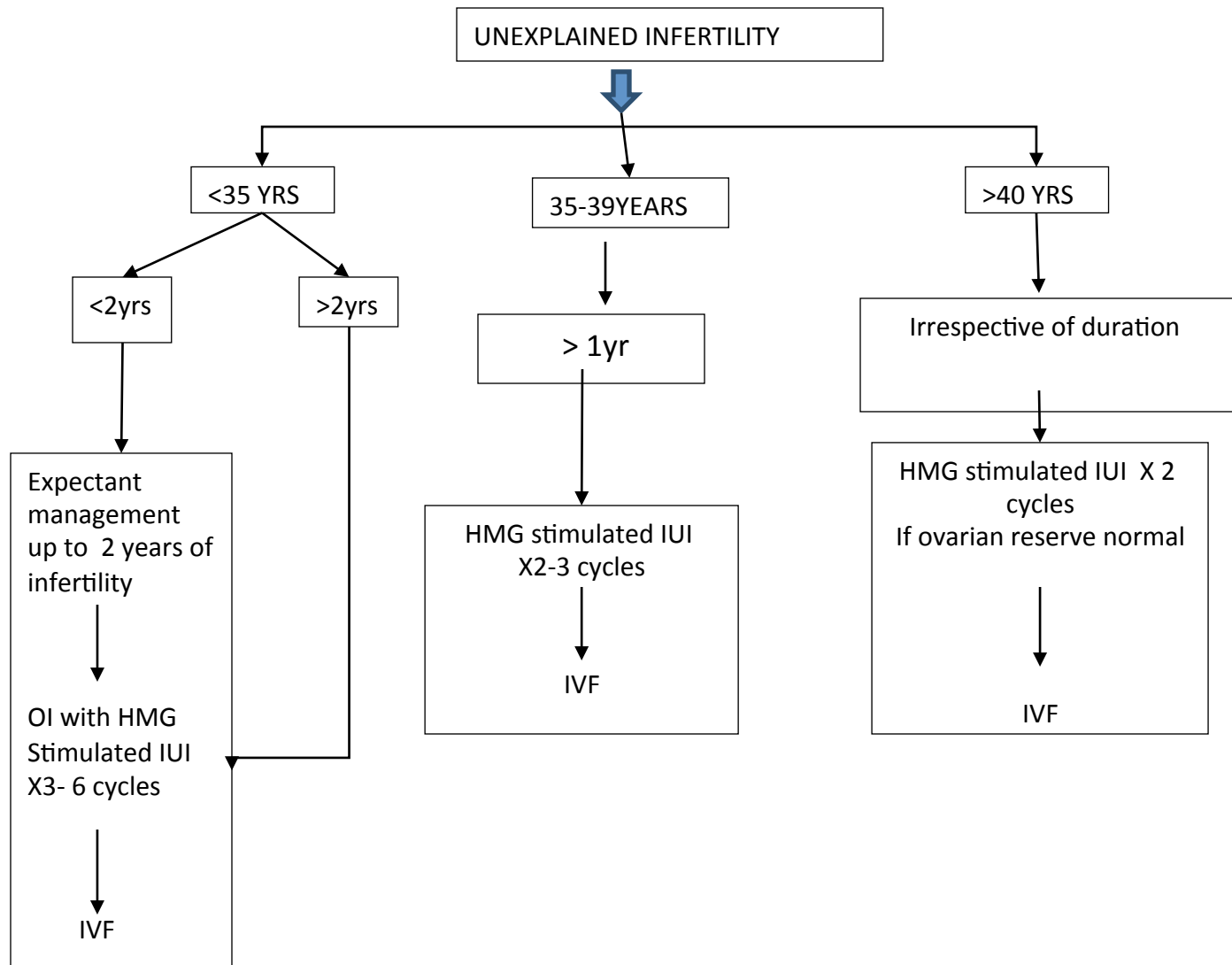


“Are we overusing IVF?”

Kamphuis et al, BMJ 2014

<u>No. (%) IVF cycles in years</u>	<u>2000</u>	<u>2011</u>	(HFEA)
Unexplained subfertility	6204 (18%)	19552 (32%)	

- IVF treatment effective in subfertility >4 years;
- **IVF no more effective than less invasive alternatives in subfertility <2.5 years;**
- IVF effectiveness unknown for subfertility 2.5-4 years



Summary

- IUI + low-dose gonadotrophin stimulation is reasonably efficient treatment for idiopathic infertility with correctly selected patients.
- IUI + gonadotrophins is more cost effective and less invasive than IVF.

Conclusion

- There is no convincing evidence to indicate that a change in policy to use IVF as the first line treatment, instead of stimulated IUI, for unexplained infertility is justified.