

Facts and fiction in ART

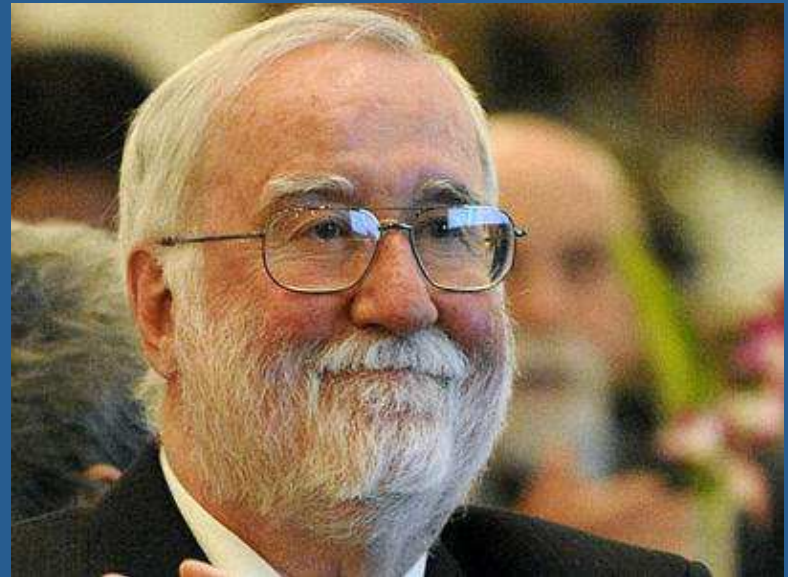
an evidence-based approach

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- In real practice doctors generally try to work using Evidence-based medicine.
- However, several procedures and drugs are being used extensively in spite of the low quality evidence or no evidence at all.

Evidence-Based Medicine
is the integration of
(patho)physiological
mechanisms and the
outcome of top-quality
clinical research



David Sackett

EMB in ovarian stimulation

Why we may abandon basal FSH testing?

- AMH is the most informative serum marker of ovarian reserve that can be assessed at any point in the cycle.
- FSH must be done early in follicular phase and normal levels of FSH do not reflect properly the ovarian reserve.
- The future role of Basal FSH testing is in doubt. (Toner and Seifer 2013)

Recombinant versus urinary gonadotropins for ovarian stimulation in ART (A Cochrane review)

- 42 trials – 9606 couples
- There was no significant difference in the live birth rate. [OR 0.97, 95% CI (0.87-1.080)].
- No difference in the incidence of OHSS [OR 1.18, 95% CI (0.86-1.61)].
- There is no significant difference in IVF outcome using any type of FSH (van Wely et al., 2011)

Letrozole versus clomid for infertility treatment in PCOS (Legro et al., 2014)

- A double-blind multicenter randomized trial
- 750 women for 5 cycles.
- Cumulative LBR was significantly higher in letrozole arm 103/374 (27.5%) versus 72/376 (19.1%) $p = 0.007$
- Four major anomalies in letrozole and only one in clomid, but difference was not significant ($p = 0.65$).

Live birth after combined adjuvant therapy for IVF/ICSI: a case controlled study

- In IVF/ICSI cycles combined treatment of aspirin, doxycycline, prednisolone, with or without oestradiol patches in 485 patients in treatment arm versus no treatment in a control of 485 patients showed no significant difference in live birth rate. (Motteram et al., 2014)

Growth hormone and poor ovarian response

- Three meta-analysis showed that co-treatment with growth hormone improves assisted reproduction outcome in poor responders.
- It does not increase the number of oocytes, probably the impaired PR is due to an effect on the oocytes.
- However, the increase in the pregnancy rate is small and the drug is extremely expensive(de Ziegler et al., 2011).

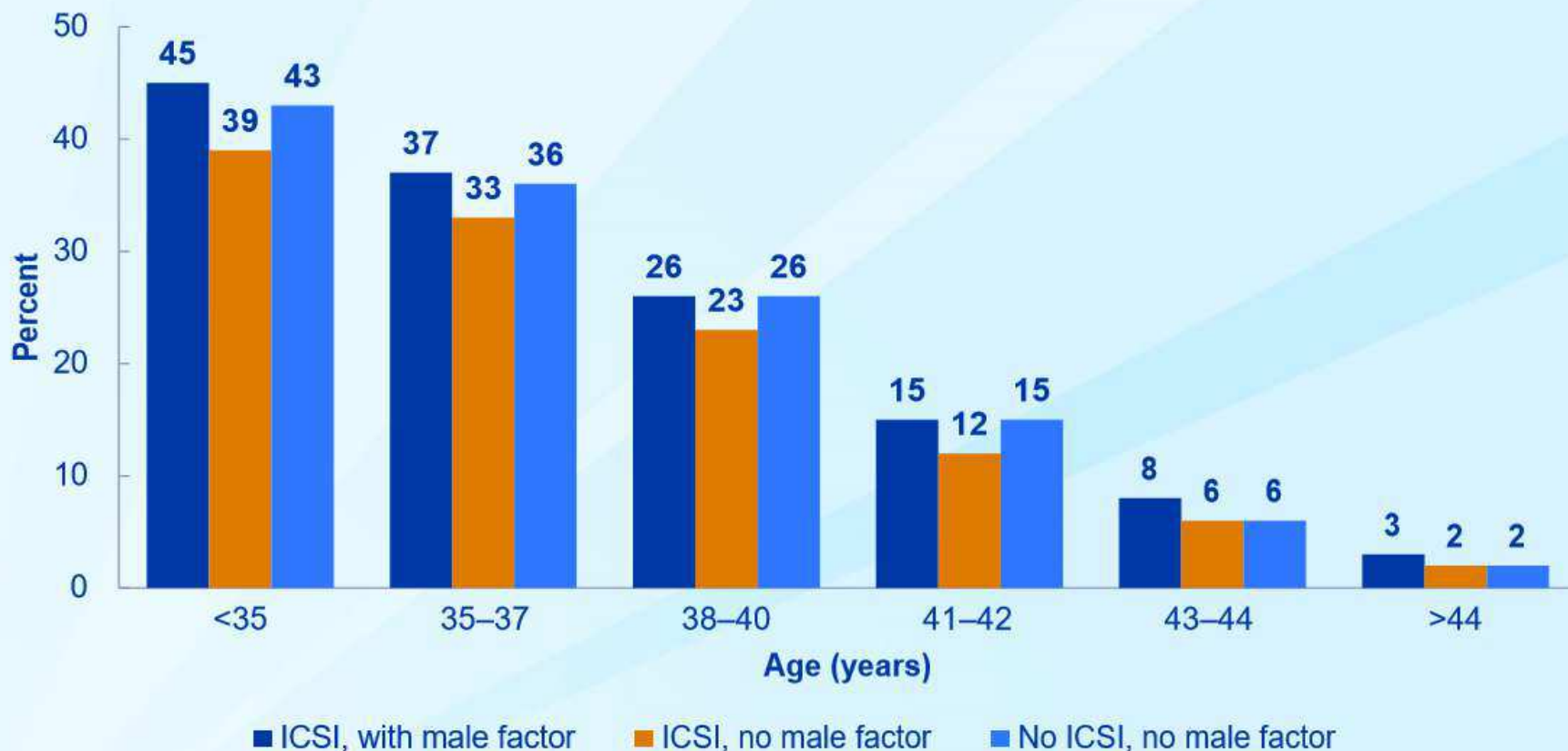
Should DHEA supplementation be used for poor ovarian response?

- Nearly 25% of IVF clinics world wide used DHEA in poor responders.
- No data is available that DHEA improves the clinical outcome in poor responders (Surkara et al., 2012).
- Its use cannot be currently recommended (Urman and Yakin2012)

A retrospective study of 362 poor responder women underwent IVF/ICSI

- The live birth rate was 6%
- The total cost per live birth was 87748 Euros (Busnelli et al., 2015)

Percentages of Fresh Nondonor Retrievals That Resulted in Live Births Among Patients with or Without Diagnosed Male Factor Infertility, by Age Group and Use of ICSI,* 2013



IVF in women above 40 years

- Clinical pregnancy rate was 12.3% (Seng et al., 2005)
- Live birth rate was 10% (De Bruker et al., 2013)
- Live birth rate was 6.7% and only 1.1% for women above 43 years (Serour 2010).

EBM in IUI

Intrauterine insemination in The Netherlands (Steures et al. 2007)

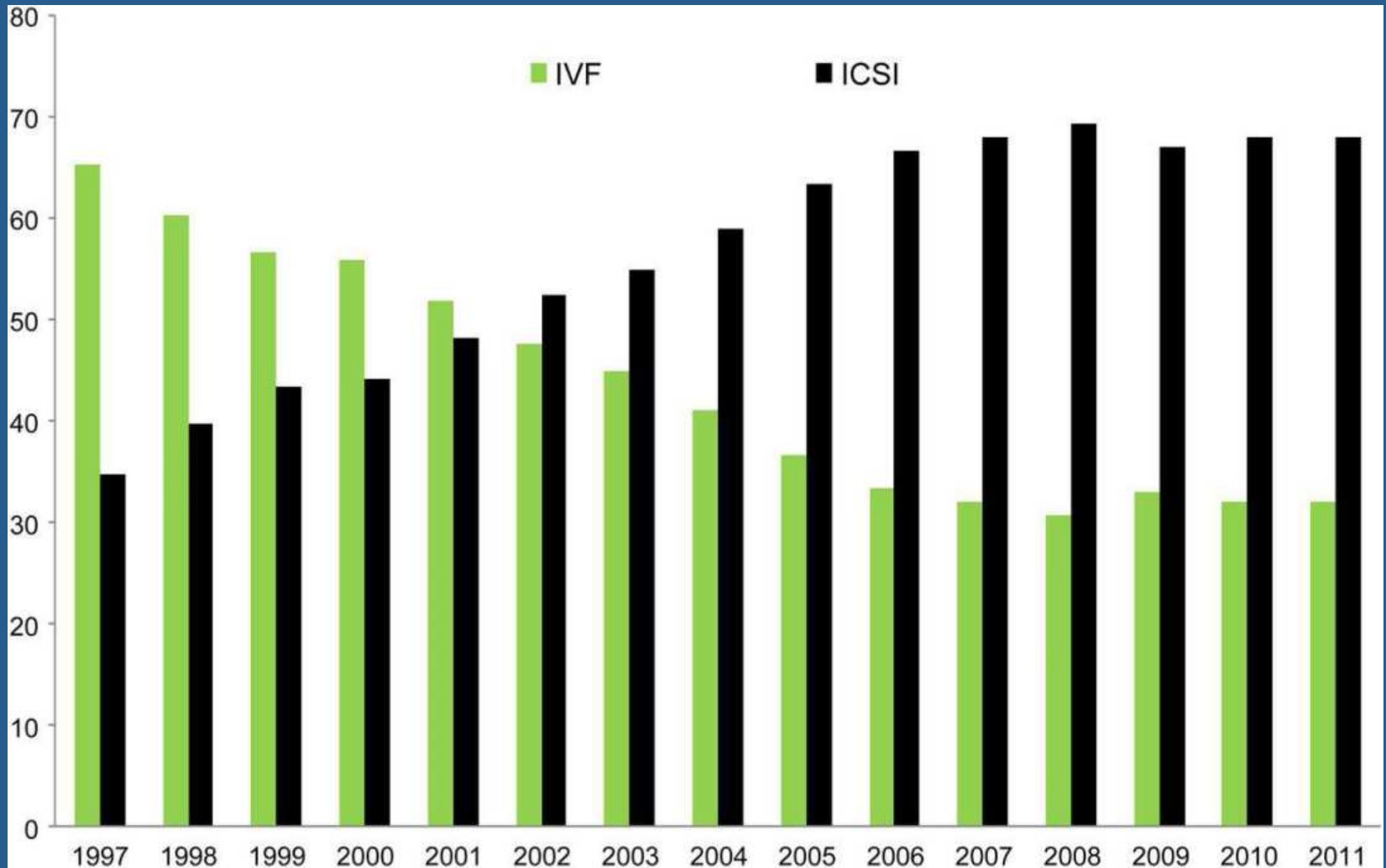
- 19,846 IUI cycles. The mean pregnancy rate per cycle was 9.0% and the ongoing pregnancy rate per cycle was 7.3%. Multiple pregnancies occurred in 9.5% of the ongoing pregnancies.
- pregnancy rate per IUI cycle in The Netherlands (9.0%) was comparable with that reported in the international literature (8.7%).

Data of ESHRE on year 2010 (published 2014)

- A total of 176512 IUI with husband semen
- Delivery rate 8.9%
- Twins 9.6%
- Triplets 8.5%

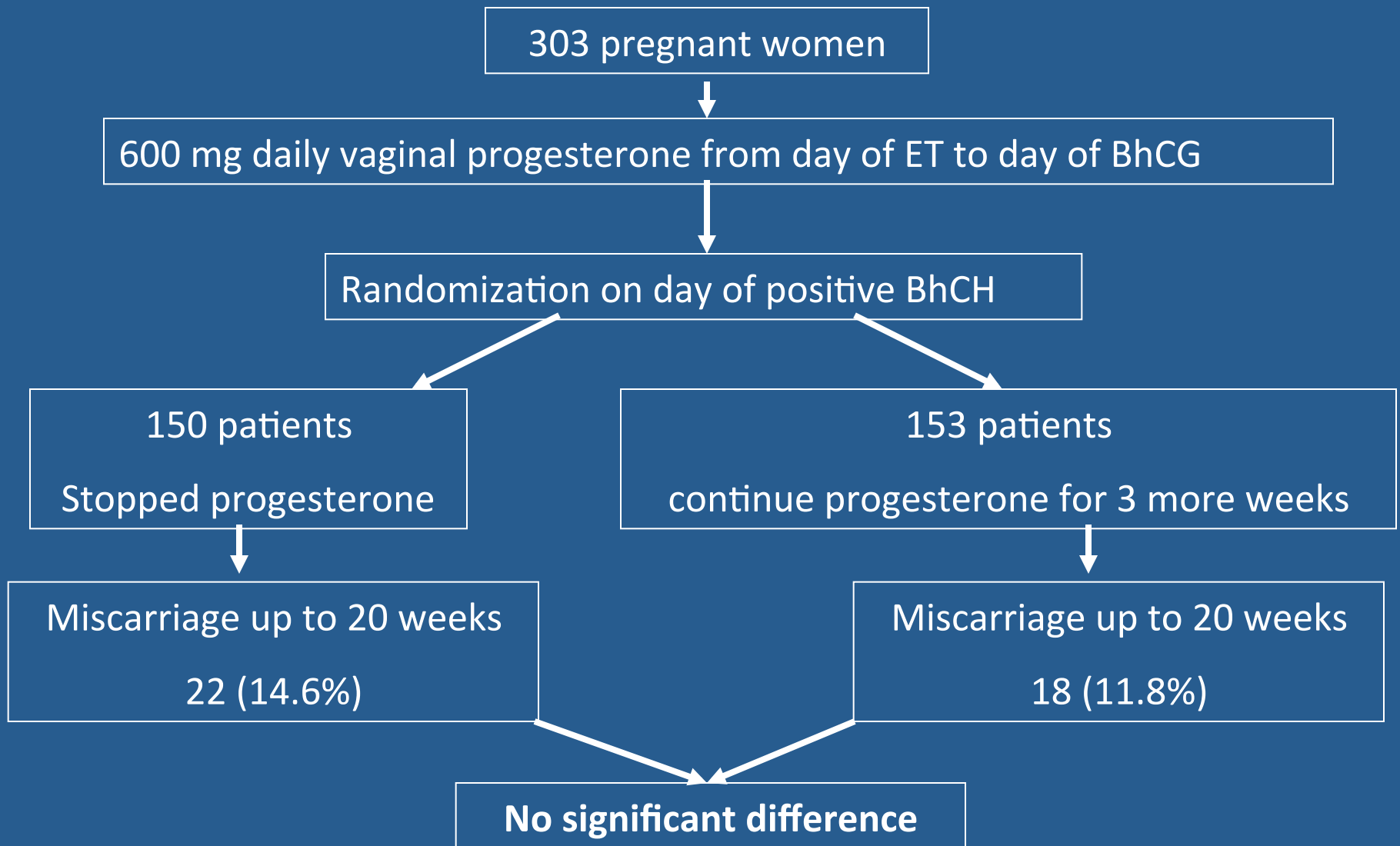
EBM in IVF/ICSI

Proportion of IVF/ICSI in Europe 1997–2011.

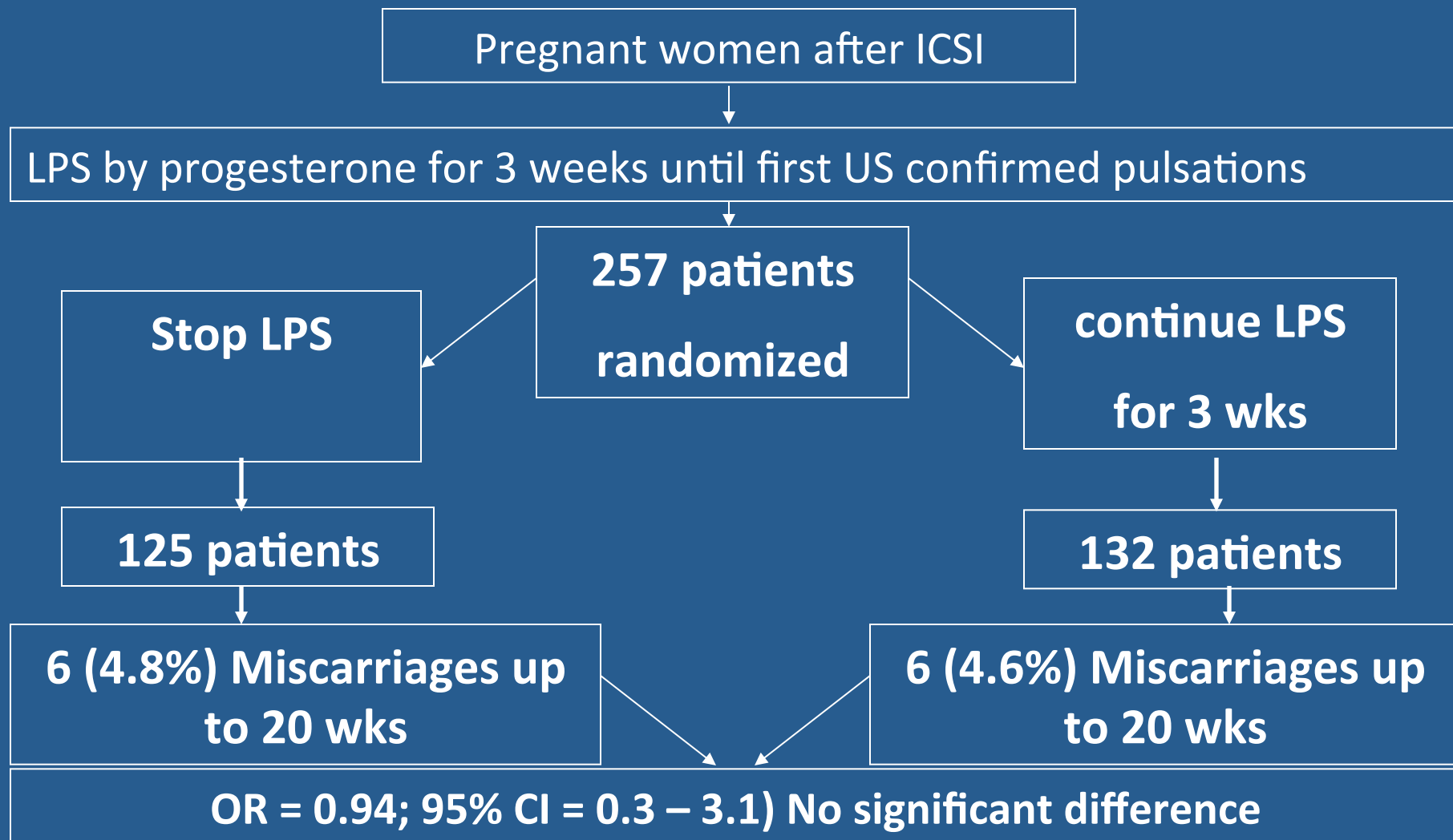


The European IVF-Monitoring Consortium (EIM) et al. Hum. Reprod. 2016;31:233-248

Stop LPS on day of BhCG vs. 3 weeks later (Andersen 2002)



Prospective randomized study comparing LPS for ICSI patients up to first ultrasound versus three weeks more
(Aboulghar et al. 2008)



Triggering ovulation with GnRH α Griesinger et al. 2006

23 Studies



Final oocyte maturation



GnRH agonist
0.5 bolous



Pregnancy rate: 0.21, 0.05-0.84, $p=0.03$
OHSS: Significant drop
First trimester pregnancy loss: 0.05
increase



hCG
10,000 IU



Higher pregnancy rate
Higher OHSS rate
Lower first trimester
pregnancy loss

GnRHa versus hCG for oocyte triggering in GnRH antagonist protocol: Cochrane Review

(Youssef et al 2011)

- 11 RCTs n = 1055
- 8 fresh antagonist studies
- GnRH agonist was less effective than hCG in term of live birth rate (0.44, 95% CI 0.29 – 0.68) and ongoing pregnancy rate (0.45, 95% CI 0.3 – 0.65)
- For a group with 30% live birthrate in hCG group, the LBR in GnRha triggering will range between 12 – 22%
- OHSS rate was significantly lower in GnRHa group (OR 0.10, 95% CI 0.01 – 0.82) for a group with 3% OHSS rate with hCG, the rate would be between 0% and 2.6% with GNRHa.

Frozen embryos and number of embryo transfer

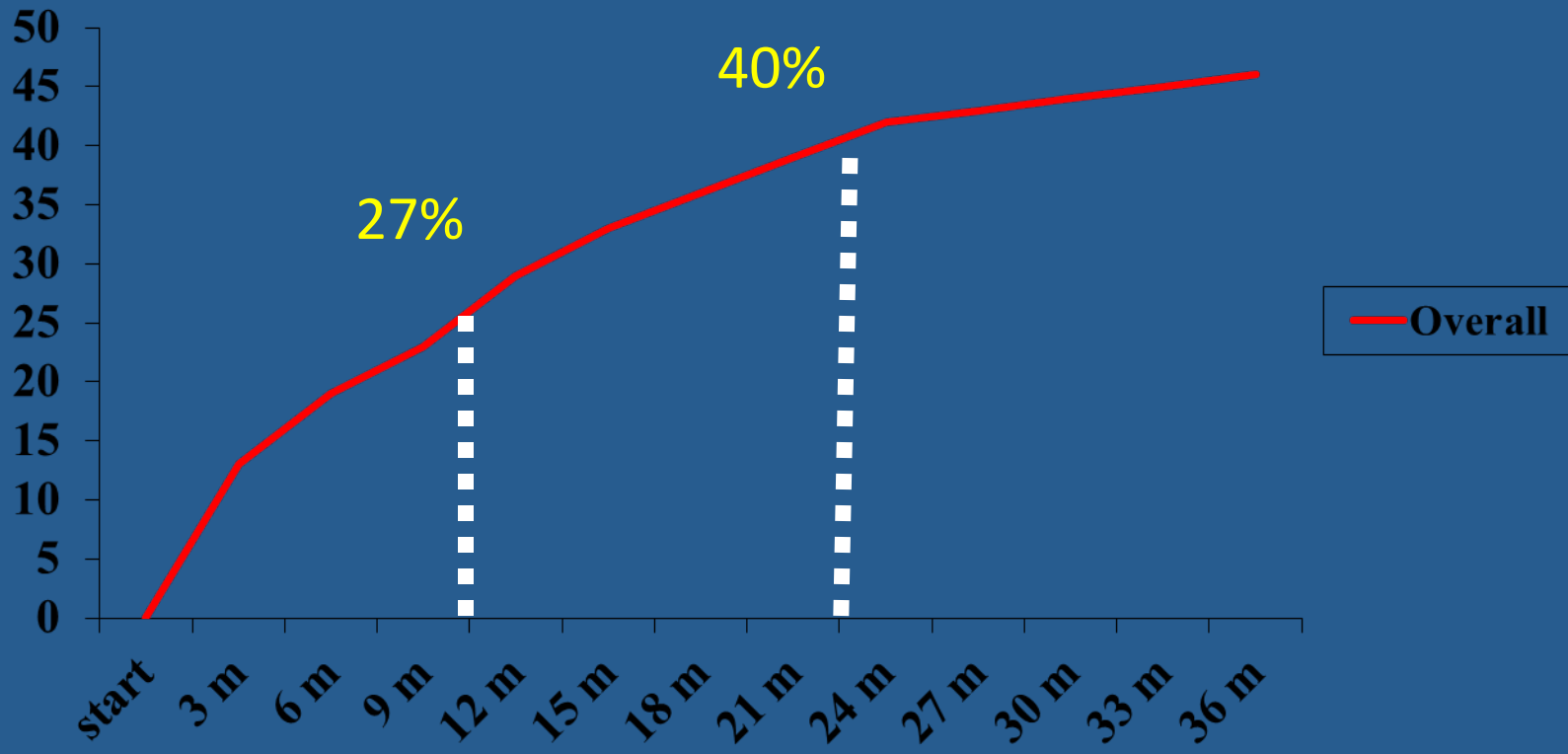
- Frozen embryos were as effective as fresh transfers in many IVF centers.
- Single embryo transfer: significantly lower PR as compared to double ET (Nardelli 2014)
- This may have implication according to the methods of financing IVF

The impact of endometrioma on IVF/ ICSI outcome: a systematic review

- Three RCT of IVF/ICSI compared women with endometrioma versus women with no endometrioma, showed no significant difference in LBR [OR 0.98; 95% CI (0.71-1.36)] or CPR [OR 1.17, 95% CI (0.87-1.58)].
- The women with endometrioma had lower number of oocytes and higher cancelation rate.
- There is no significant difference in CPR and LBR between women who underwent excision of endometrioma versus no surgery (Hamadan et al., 2015)

Improving live BR

Untreated unexplained subfertility



Intramural fibroids with cavity involvement

- No prospective randomized studies available.
- No high quality evidence.

Intramural fibroids without endometrial cavity involvement and IVF outcome (A systematic review and meta-analysis)

Sunkara et al., 2010

- 19 observational studies.
- 6087 IVF cycles
- Significant decrease in live birth rate in women with fibroids $P = 0.002$

Aspirin and/or heparin for women with unexplained recurrent miscarriage (A Cochrane review 2014)

- 1228 women with or without inherited thrombophilia were randomized for anti-coagulants versus placebo.
- No benefit of anticoagulants on live birth rate regardless which anticoagulant was used.
- Preterm labour, preeclampsia, IUGR were not significantly affected by any treatment regimen.
- The Cochrane review does not support the use of anti-coagulants in women with unexplained recurrent miscarriage (De Jong et al., 2014)

Effect of heparin on IVF outcome

A systematic review

- Meta-analysis of randomized studies showed no difference in clinical pregnancy rate (RR 1.23, 95% CI 0.97-1.57) as well as the live birth in women randomized between heparin versus placebo (Seshadri et al., 2012)

Heparin for IVF (Cochrane Review)

- 386 women who were randomized are included in the meta-analysis. They receive heparin versus placebo or no treatment.
- There was no difference in the clinical pregnancy rate OR 1.85; 95% CI 0.8-4.24 or live birth rate OR 1.6; 95% CI 0.94-2.9
- Adverse effects were inadequately reported (Akhtar et al., 2015)

At present there is no evidence that the use of anticoagulants in repeated miscarriage in the presence of inherited thrombophilia is effective. However, further randomized studies may be done in this subgroup of patients. (de Jong et al., 2014)

EBM in male infertility

Surgery for varicocele in subfertile men: (A Cochrane review) (Evers et al., 2009)

- Eight randomized studies comparing the outcome for varicocelectomy versus no surgery
- Showed: OR 95%, CI 0.73 – 1.68 indicating no benefit for varicocelectomy.

Surgery of varicocele in subfertile men

Kroese 2012

- Ten studies, 894 men, no studies reported live birth.
- OR 95% CI 1.05-2.05
- There is evidence that varicocelectomy may improve couples' chance of pregnancy, however, the evidence is low.

Future of varicocelectomy

- All andrologists feel a prospective study on varicocelectomy is important (Trussell et al., 2014)
- Most results are retrospective and poor quality.
- Randomized trials are conflicting and methodologically poor.

Varicocelectomy

Trussell et al., 2014

- A planned randomized study of microgurgical varicocelectomy versus no treatment of male factor was planned to start in 5 US major centers.
- All 5 centers failed to recruit adequate number of patients because:
 - Lack of interest of urologists.
 - Previous medical treatment for the male.
 - Lack of interest of placebo arm.

Pre-implantation genetic screening

All agree that PGS using cleavage stage biopsy by (FISH) is not useful or cost effective

- The new techniques where biopsy is taken from blastocysts and all 24 chromosomes will be studied, will it change really anything or we are simply going back to the future?
(Mastenbroek and Pepping 2014)

Clinical outcome following PGS with time lapse monitoring: a systematic review (2014)

- TLM is a semi-quantitative technology of embryo morphology and developmental Kinetics in ART
- 13 eligible studies
- No single morphokinetic parameter has been shown to predict implantation potential.
- There are currently no high quality data to support the clinical use of TLM in IVF/ICSI.
(Kaser and Racowsky, 2014)

Time laps systems versus traditional incubation for IVF

- Three randomized studies including 994 women demonstrated no conclusive evidence of a difference in LBR [OR 1.1, 95% CI (0.45-2.73)]
- No difference in clinical pregnancy rates [OR 1.23, 95% CI (0.96-1.59)]
- No difference in miscarriage rate [OR 0.7, 95% CI (0.47-1.04)]
- There is insufficient evidence that TLS improves the IVF outcome (Armstrong et al., 2015)

FDA warning against PGS

- In November 2013 FDA sent a warning letter to the manufacturers of the equipment which test the 23 chromosomes for PGS.
- The opponents thought that FDA is overcautious and violates consumer rights.
- The proponents supported the agency that this is an unclassified medical device and the agency's action is protection of consumers.
- (Yim and Chung et al., 2014)

PGS still in search of a clinical application: a systematic review

- PGS is an unproven and still experimental procedure which until evidence suggests otherwise, should only be offered under study conditions. (Gleicher et al., 2014)

Array-comparative genomic hybridization (Array-CGH) studies 24 chromosomal anomalies by a biopsy taken from the blastocyst, it takes 2 days for results to detect aneuploidy embryos.

Next generation sequencing (NGS) use the same biopsy but it is much faster (Florentino et al., 2014)

The clinical effectiveness of PGD for aneuploidy of all 24 chromosomes

- Three randomized studies demonstrated benefit in young and good prognosis patients in terms of clinical pregnancy rate and the use of single embryo transfer.
- However, studies in advanced maternal age, recurrent miscarriage and implantation failure did not show improvement

(Lee et al., 2015)

Randomized study comparing
array-CGH with NGS demonstrated
that NGS is a reliable methodology
(Florentino et al., 2014)

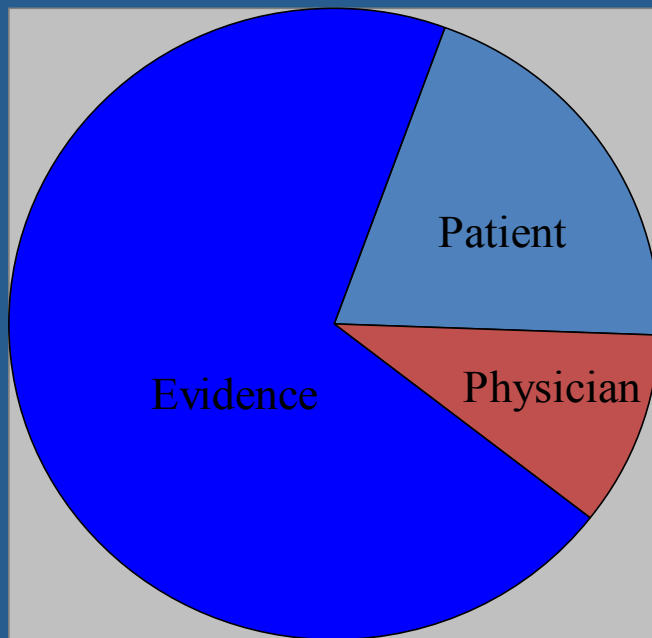
Cost effectiveness analysis of PGS versus expectant management in patients with unexplained recurrent pregnancy loss

IVF/PGS with 24-chromosome screening versus expectant management
(Murugappan et al., 2015)

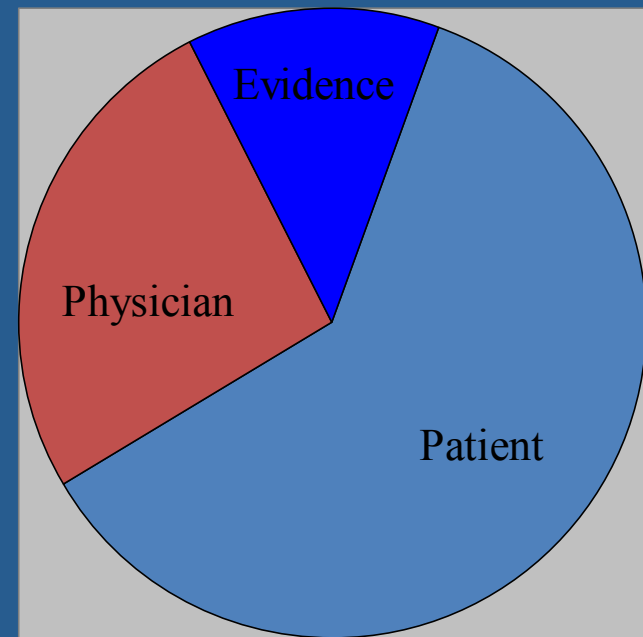
	IVF/PGS	Expectant treatment
Live birth rate	53%	67%
Clinical miscarriage rate	7%	24%
Cost per live birth	45300\$	418\$

Clinical reasoning: different scenarios

1 Cancer treatment



2 Infertility treatment



ENT specialist views on tonsillectomy

Children	TE advised	Remain
1000	32%	676
676	34%	432
432	28%	311

Bakwin, H.: NEJM 232: 691-697, 1945

Conclusions (1)

- It is important that all infertility specialists follow evidence-based medicine.
- High quality research is required in grey areas where there is no clear evidence available.
- All new infertility techniques, particularly the very expensive ones should be evaluated completely before being used in clinical practice.

Conclusions (2)

- Studying 24 chromosomes by NGS technique is a fantastic introduction to medicine.
- We need more research for this technology:
 - To confirm the value for its use by randomized studies.
 - To reduce the expenses.