Personalised medicine in reproduction

Prof. Dr. Bart CJM Fauser
Disclosure of interest, Fauser

- Professor of Reproductive Medicine
- Chair, WHO steering committee infertility guidelines
- Board member Dutch Medical Research Counsel
- Chief Editor Reproductive Biomedicine Online
- COGI chair
- Executive boards international organisations
- Consultant various pharmaceutical companies
- Visiting professor at different international institutions
The era of personalised medicine

Developments in clinical research

The Precision Medicine Initiative
A New National Effort JAMA 2015

Assessing the Gold Standard — Lessons from the History of RCTs
Laura E. Bothwell, Ph.D., Jeremy A. Greene, M.D., Ph.D., Scott H. Podolsky, M.D., and David S. Jones, M.D., Ph.D.

Integrating Randomized Comparative Effectiveness Research with Patient Care
Louis D. Fiore, M.D., M.P.H., and Philip M. Hartwig, M.D.

Population and Personalized Medicine in the Modern Era JAMA 2014

The Science of Choosing Wisely — Overcoming the Therapeutic Illusion NEJM 2016

A New Initiative on Precision Medicine
Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

Why Most Clinical Research Is Not Useful 2016
John P. Ioannidis

Precision Medicine — Personalized, Problematic, and Promising
J. Larry Jameson, M.D., Ph.D., and Dan L. Longo, M.D.
Population and Personalized Medicine in the Modern Era

Classic health care research has centered on studying a group of individuals and then extrapolating the findings to the general population. In this context, evaluating response. In addition, some fac individual metabolizes a medi tinlatelet agent clopidogrel is:

Tools Being Used in Clinical Research to Understand Population and Personalized Medicine

- Expanded Data Capture
  - Advanced diagnostics
  - Genomics
  - Proteomics
  - Metabolomics
  - Imaging
  - Electronic health records
  - Demographics
  - Family history
  - Medications
  - Diagnoses
  - Procedures
- Mobile digital technologies
  - Lifestyle
  - Socioeconomic data
  - Environmental data
  - Physical activity

Clinical Research

- Nonrandomized Exposures
  - Study Sample
  - A
  - B
- Randomized to Exposures
  - Study Sample
  - Exposures
  - A
  - B
- Outcomes

Expanded Data Sources

- International registries and trials, such as
  - UK Biobank
  - Health eHeart
  - PatientsLikeMe
- American Heart Association Cardiovascular Genome Phenome Study

Population Medicine

Personalized Medicine
Current evidence based medicine paradigm

Patient population

A

B

EBM

95% CI difference

difference
Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, M.D., J.C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, M.D., Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, Ph.D., e Network*

A All Patients

N=750
P=0.01

Live Birth (%)

Days from Randomization to Live Birth

Letrozole

Clomiphene
Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome

Richard S. Legro, M.D., Robert G. Brzyski, M.D., Ph.D., Michael P. Diamond, M.D., Christos Coutifaris, M.D., Ph.D., William D. Schlaff, M.D., Peter Casson, M.D., Gregory M. Christman, M.D., Hao Huang, M.D., M.P.H., Qingshang Yan, Ph.D., Ruben Alvero, M.D., Daniel J. Haisenleder, Ph.D., Kurt T. Barnhart, M.D., G. Wright Bates, M.D., Rebecca Usadi, M.D., Scott Lucidi, M.D., Valerie Baker, I. C. Trussell, M.D., Stephen A. Krawetz, Ph.D., Peter Snyder, M.D., Dana Ohl, Nanette Santoro, M.D., Esther Eisenberg, M.D., M.P.H., and Heping Zhang, I. e Network*
Standard vs tailored approach in medicine

Herceptin, Breast cancer
Paradigm shift from evidence based to patient tailored medicine (2)

Patient population

- Homogeneous
- Heterogeneous

Standardized phenotyping

Intervention

Primary Outcome

EBM

PTM

95% CI difference

Multi-variate prediction models
Figure 1. Types of prediction model studies covered by the TRIPOD statement.

- Only a single data set is available: All data are used to develop the model
  - Type 1a: Development only
- Only a single data set is available: A portion of the data are used to develop the model
  - Type 1b: Development and validation using resampling
  - Type 2a: Random split-sample development and validation
  - Type 2b: Nonrandom split-sample development and validation
- Only a single data set is available: A separate data set is available for validation
  - Type 3: Development and validation using separate data
  - Type 4: Validation only
The EBM paradigm

- Meta analysis
  - IPD Meta analysis

- Experimental
- Observational

- Level 1: RCTs*
- Level 2: Cohort Studies
- Level 3: Case-Controlled Studies
- Level 4: Case Series
- Level 5: Case Report or Expert Opinion

* RCT = Randomized Clinical Trial
Examples of personalised care in infertility

Previous attempts to individualise infertility care have been based around:

- Ongoing pregnancy chances in unexplained infertility
- CAT serum test association with tubal infertility
- Live birth following ovulation induction in PCOS
- Markers for ovarian reserve / response to stimulation
- Markers for implantation failure (gene expression, microbiome)
- Prediction of pregnancy complications & child outcomes in PCOS
Validation of a model predicting spontaneous pregnancy among subfertile untreated couples

Claudine C. Hunault, M.D., M.Sc., Marinus J. C. Eijkemans, M.Sc., Egbert R. te Velde, M.D., Ph.D., John A. Collins, M.D., and J. Dik F. Habbema, Ph.D.

<table>
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<th>Female age (yrs)</th>
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<td>Secondary care couple</td>
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<td>Tertiary care couple</td>
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</table>

Habbema, Hum Reprod 2015
Hunault, Hum Reprod 2005
Hunault, F&S 2002
Eimers, F&S 1994
Collins, F&S 1989
CC for ovulation induction in PCOS

Ovulation

Pregnancy (35-40%)
# Prediction Medicine, methodology

## Prospective, cohort follow-up study

- Single or no (natural cause of disease) intervention
- Define primary (or composite) endpoint
- Univariate association analysis
- Multi-variate analysis (preferably no more than 10 variables)
- Development prediction model

## External validation prediction model

### Predictors of Patients Remaining Anovulatory during Clomiphene Citrate Induction of Ovulation in Normogonadotropic Oligoamenorrheic Infertility

BABEK IMANI, MARINUS J. C. EIJKEMANS, EOBERT R. TE VELDE, J. DIK F. HABEMA, AND BART C. J. M. FAUSER

JCEM 1998

![AUC 0.84](image)
CC ovulation induction in WHO 2 - outcome prediction

Nomogram; live birth (age, BMI, cycle, FAI)

Required screening information
- Amenorrhea or oligomenorrhea
- BMI (kg/m²)
- FAI (T x 100/SHBG)
- Age (y)

Chance of ovulation (%)

80 (70-88)
60 (52-69)
50 (42-59)
40 (33-49)
30 (24-40)
20 (14-30)
10 (5-20)
5 (1-16)

Chance of a live birth (%)
(95% CI)
Predictors of Pregnancy in Women with Polycystic Ovary Syndrome


- n=626
- RCT; CC, Metformin, or both up to 6 cycles
- Baseline characteristics and prediction of: ovulation, conception, pregnancy, live birth
- FAI, BMI, Proinsulin, duration attempting conception

Predicting Pregnancy in Women with Polycystic Ovary Syndrome

J Clin Endocrinol Metab, September 2009, 94(9):3183–3184

B. C. J. M. Fauser and M. J. C. Eijkemans
Ovarian stimulation for IVF is NOT controlled

Hyperresponse = danger
Hyporesponse = poor outcome

Ovarian response prediction
- Female age
- AFC
- Body weight
- AMH
AMH and its potential clinical applications

- Cancer treatment
- Fecundity
- IVF
- POI
- PCOS
- Anorexia
- GC tumours
- Ovarian surgery
- Menopause

AMH
Added value of ovarian reserve testing on patient characteristics in the prediction of ovarian response and ongoing pregnancy: an individual patient data approach

Simone L. Broer1,2,*, Jeroen van Disseldorp1,2,*, Kimiko A. Broeze1,2,

Poor response (<5 oocytes)
(28 studies; n=5,705 women)

Excessive response (>15)
(57 studies; n=4,786)

AUC AMH 0.81
AUC AMH 0.82
Steps towards individualised ovarian stimulation for IVF

Same starting dose of gonadotrophin to all patients associated with efficacy or safety concerns for some patients

- Highest efficacy
- Risk of low efficacy
- Risk of safety concerns and cancellation of transfer

Number of patients vs Number of oocytes
Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial

Conclusion

Individualised dosing
More often desired oocyte No
Complementary approaches
- evidence vs patient based medicine

EBM ↔ PBM

- Treatment focus
- Multiple interventions
- RCT
- Homogenous pt population
- Patient/context focus
- Single intervention
- Cohort, follow-up
- Heterogeneous pt population