PRE-CONGRESS COURSE 1

Targeting and managing special patient groups - including hands-on workshop in trophectoderm biopsy

Paramedical Group
Munich - Germany, 29 June 2014

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Targeting and managing special patient groups - including hands-on workshop in trophectoderm biopsy

Munich, Germany
29 June 2014

Organised by
The ESHRE Paramedical Group

Contents

Course coordinators

Helle Bendtsen (Denmark)

Course description

This advanced course is aimed to give an update on the current theoretical background, hands on treatment and support for patient with endometriosis, genetic disorders and recurrent miscarries. There will be an interactive session in counseling focusing on nurses and midwifes and counselors working in a fertility clinic.

For the delegates working in the lab there will be a practical demonstration and hands-on workshop in trophectoderm biopsy. This workshop will summarize the most important aspects of successful trophectoderm biopsy: pre-treatment of the embryo, timing of biopsy, coordinated use of laser and micro manipulator and tips for most convenient biopsy. The technique will be demonstrated on mouse blastocysts. Depending on tome participants will also be able to do practical exercises

Target audience

Nurses, midwifes, counsellors, clinical embryologist and lab technicians

Scientific programme

Chairmen: Helle Bendtsen (Denmark) and Inge Rose Joergensen (Denmark)

09:00 - 09:10 Introduction
Helle Bendtsen - Denmark

Session 1: Endometriosis and PCOS

09:10 - 09:35 Endometriosis and infertility: patient-tailored treatment options
Carla Tomassetti - Belgium
09:35 - 10:00 The promise of IVM for the treatment of infertility in patients with PCOS
Michel De Vos - Belgium

Session 2: Genetic

10:00 - 10:25 Counseling for genetic disorders
Cath King - United Kingdom

10:30 - 11:00 Coffee break

11:00 - 11:25 Microarray tools for PGD: an introduction
Martine De Rycke - Belgium

Session 3: Miscarriage

11:25 - 12:00 Is trophectoderm biopsy and subsequent PGD the new tool for embryo selection for a subgroup of patients?
Mandy Katz-Jaffe - U.S.A.
12:00 - 12:30 Dealing with miscarriage
Anne Louise Lunoe - Denmark

12:30 - 13:30 Lunch

13:30 - 15:15 Hands on session in "Trophectoderm biopsy" (laboratory)

13:30 - 15:15 Interactive session in counseling (Nurses, midwifes and counsellors)
13:30 - 14:15 Supporting women during waiting periods
Hetty Ockhuysen - The Netherlands
14:30 - 15:15 Decision aid on the type of medication
Eline Dancet - Belgium

15:15 - 15:45 Coffee break

15:45 - 16:30 The fine line of support and pressure - The role of family and friends
Helga Sol Olafsdottir - Iceland

16:40 - 17:00 Closing

Endometriosis and infertility: patient-tailored treatment options

Dr. Carla Tomassetti
Leuven University Fertility Center - Dept. gynaecology and obstetrics

- No conflicts of interest
- Research supported by Clinical Research Funds of University Hospitals, Leuven
- LUFc receives unrestricted research grants from Ferring Pharmaceuticals and Merck Serono

Meuleman C, Tomassetti C, D'Hoore A, Wolthuis A, Van Cleynenbreugel B, Laenen A, Penninckx F, Vergote I, D'Hooghe T

Endometriosis Fertility Index (EFI)

- Endometriosis and infertility
- EFI
- Validation of EFI

Endometriosis and infertility

- Monthly fecundity rate:
  - Normal couple: 15-20% (age)
  - untreated endometriosis: 2-10%
- Biological mechanisms as explanation?
  - Distorsion of pelvic anatomy: adhesions!
    - Egg pickup and transport
  - Peritoneal (fluid) changes eg. Inflammatory cytokines
  - Hormonal, endocrine and ovulatory changes
  - Implantation function (eutopic endometrium)
  - Egg/embryo quality (egg donation model)
  - Utero-tubal transport (contractility)
  - Dyspareunie and coïtus frequency

Endometriosis and infertility

Effect of hormonal therapy on fertility:

ESHRE Eosis guidelines 2013

Recommendation	
In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes, et al., 2007).	A
In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness, et al., 2004).	A

Endometriosis and infertility

- Effect of surgery for endometriosis:
  - rAFS I-II: Cochrane (Jacobson 2007):

    Meta-analyse of 2 RCT's with opposit result
    - Canadian (Marcoux 1997) n=341 <-> Gruppo Italiano (1999) n=101
      ZS: OR 2.03, 95%CI 1.28-3.24 OR 0.76, 95%CI 0.31 to 1.88
      ZS >20w: OR 1.95, 95%CI 1.18-3.22 livebirth OR 0.85, 95%CI 0.32 to 2.28
  - Combination ongoing and live birth: improvement of fertility : OR 1.64, 95% CI 1.05 to 2.57; NNT = 12
  - ESHRE guideline 2013

Recommendations

In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriotic lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Jacobson, et al., 2010, Nowroozi, et al., 1987).	A
In infertile women with AFS/ASRM stage I/II endometriosis, clinicians may consider CO2 laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporisation is associated with higher cumulative spontaneous pregnancy rates (Chang, et al., 1997).	C

Endometriosis and infertility

- Effect of surgery for endometriosis :
  - rAFS III-IV: no gerandomised data

In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart, et al., 2008).	A
The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.	GPP
In infertile women with AFS/ASRM stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat, et al., 1989, Vercellini, et al., 2006a).	B

Endometriosis and infertility

- Effect of surgery for endometriosis rAFS III-IV:

Colorectal involvement: systematic Review - Meuleman et al 2011 Hum Reprod Update

Outcome variables	49 studies: bowel resection 32 – mixed 16 3894 patients: bowel resection 73% - full thickness disc excision 10% - superficial surgery 17%	Results
Postoperative complications (major)	94% (46/49)	0% - 43%
Pain	67% (33/49) Mean/median follow-up < 24mths: 17/33 **≠ measuring & reporting symptomatic efficacy** Patient based VAS: 6/33	**Improvement** pain, gynaecologic & digestive symptoms
Quality of life	10% (5/49) **≠ measuring & reporting symptomatic efficacy**	**Improvement** (significant)
Recurrence	43% (21/49)	**10%** (>2 years follow-up) **bowel: 2,5% / mixed: 5,7%**
Fertility	37% (18/49) Number of patients wishing to conceive – time period to conceive? Life table analysis: 3/18	24% - 57% Spontaneous: 45% Medically assisted: 55%

ENDOMETRIOSIS FERTILITY INDEX (EFI)

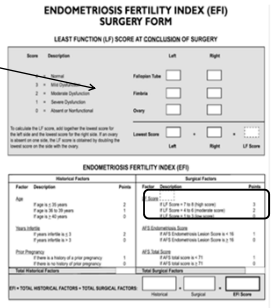
Endometriosis Fertility Index (EFI)

- 2010, Adamson & Pasta:
  - Prospective collection of data and fertility outcome (n=579, 275 variables)
  - Deduction of a new staging system by combining the most predictive variables
  - Validation on a subsequent prospective series (n=222)
- EFI = clinical instrument to predict non-ART pregnancy rates in patients after endometriosis surgery (any rAFS-stage) via:
  - Historical factors
  - Adnexal function (at the END of the surgery)
  - Extensiveness of the endometriosis
- Score 0 to 10

Adamson and Pasta, Fertil Steril, 2010

Endometriosis Fertility Index (EFI)

- Adnexal factors: 'least function (LF) score'
  - Tuba
  - Fimbriae
  - Ovary
- Fallopian tube
  - Movement of the tube over the ovary
  - Transport of sperm to the uterus
  - Initial localisation of the embryo
  - Transport of the embryo to the uterus
- Fimbriae
  - Egg pickup function
- Ovary:
  - Egg stock, folliclematuration, ovulation
  - Accessibility to fimbriae


ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Adamson and Pasta, Fertil Steril, 2010

EFI: least function score

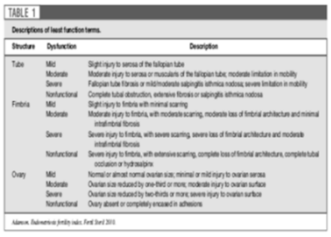
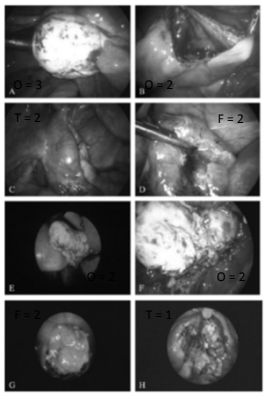


TABLE 1

Descriptions of least function terms.

Structure	Dysfunction	Description
Tube	Mild	Slight injury to serosa of the fallopian tube
	Moderate	Moderate injury to serosa or muscularis of the fallopian tube; moderate limitation in mobility
	Severe	Fallopian tube fibrosis or mild/moderate salpingitis isthmica nodosa; severe limitation in mobility
	Nonfunctional	Complete tubal obstruction, extensive fibrosis or salpingitis isthmica nodosa
Fimbria	Mild	Slight injury to fimbria with minimal scarring
	Moderate	Moderate injury to fimbria, with moderate scarring, moderate loss of fimbrial architecture and minimal intrafimbrial fibrosis
	Severe	Severe injury to fimbria, with severe scarring, severe loss of fimbrial architecture and moderate intrafimbrial fibrosis
	Nonfunctional	Severe injury to fimbria, with extensive scarring, complete loss of fimbrial architecture, complete tubal occlusion or hydrosalpinx
Ovary	Mild	Normal or almost normal ovarian size; minimal or mild injury to ovarian serosa
	Moderate	Ovarian size reduced by one-third or more; moderate injury to ovarian surface
	Severe	Ovarian size reduced by two-thirds or more; severe injury to ovarian surface
	Nonfunctional	Ovary absent or completely encased in adhesions

Adamson, Endometriosis fertility index. Fertil Steril 2010.



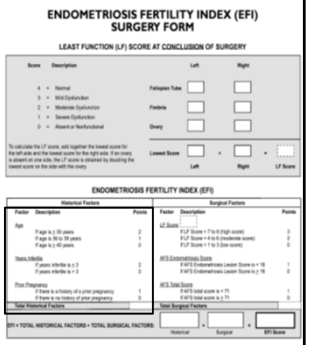
Adamson and Pasta, Fertil Steril, 2010

Endometriosis Fertility Index (EFI)

- Historical factors:
  - age
  - Duration of infertility
  - Obstetrical history

~~Male~~
previous endo-R\
Diagn test results

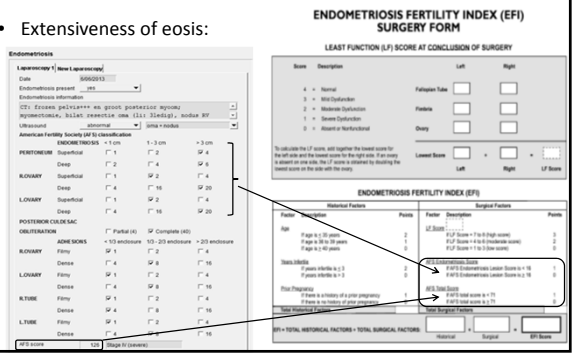
'it is required that male and female gameters are sufficiently functional' (Adamson, 2013)



Adamson and Pasta, Fertil Steril, 2010

Endometriosis Fertility Index (EFI)

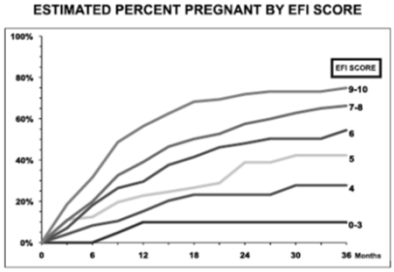
- Extensiveness of eosis:



Endometriosis Fertility Index (EFI)

Adamson
2010, Fertil Steril

Grouping



VALIDATION OF THE EFI

Validation of the EFI

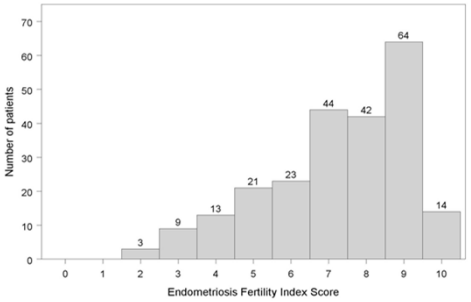
- Leuvens Universitair Fertiliteitscentrum
  Tomassetti et al, Hum Reprod 2013
- Retrospective cohort study: external validation
  - Prospectively maintained database
  - EFI retrospectively calculated in December 2011
- Sept 2006 – Sept 2010
- 326 patients with immediately postoperative child wish
  - 233 patients in non-ART
    - expectant, stim + timed coitus, stim + IUI
  - 93 direct ART (IVF, ICSI, embryo- or egg-reception)

Validation of the EFI
Tomassetti et al, Hum Reprod 2013

	N data available	N/total (%)	Mean (+/- SD)	Median (min-max)
Age at surgery (years)	233		31.3 (+/-3.9)	31 (23.1 – 42.5)
<= 35 y*		202/233 (86.7%)		
36-39 y*		29/233 (12.45%)		
>= 40y*		2/233 (0.86%)		
At least 1 previous therapeutic surgery for endometriosis [1]	233	115/233 (49.36%)		
At least 1 previous failed IUI [2] cycle	233	46/233 (19.74%)		
At least 1 previous failed ART [3] cycle	233	22/233 (9.44%)		
Duration infertility (months)	233		27.3 (+/-18.9)	24 (1 – 120)
>3 years*		56/233 (24.03%)		
<=3years*		177/233 (75.97%)		
Prior pregnancy	233			
No*		174/233 (74.68%)		
Yes*		59/233 (25.32%)		
Least function score [4,*]	233		5.7 (+/- 1.8)	6 (1-8)
High score (7-8)*		85/233 (36.48%)		
Moderate score (4-6)*		121 (51.93%)		
Low score (1-3)*		27/233 (11.59%)		
AFS endometriosis lesion score[5]	233		14.6(+/- 11.8)	10 (1-52)
<16*		155/233 (66.52%)		
>=16*		78/233 (33.48%)		
AFS total score [6]	233		40.7 (+/-31.8)	36 (1-126)
<16	233	75/233 (32.19%)		
>=16		158/233 (67.81%)		
<71*		190/233 (81.55%)		
>=71*		43/233 (18.45%)		
Partner with normospermia [7]	197	106/197 (53.81%)		
Sperm of partner: TMC [8]	189		27.7(+/-25)	20 (0 – 117)

Validation of the EFI

Distribution of patients per EFI score Tomassetti et al, Hum Reprod 2013

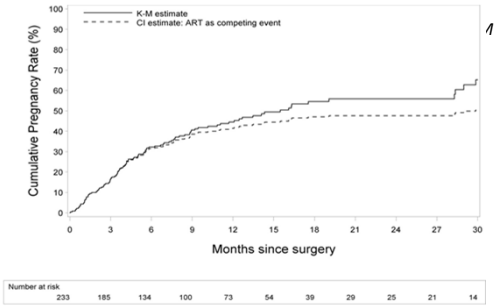


Validation of the EFI

- Statistical analyses:
  - Life table analyse (Kaplan-Meier), cumulative incidence rates (CI)
  - 6 EFI subgroups as in original article by Adamson+Pasta (0-3,4,5,6,7+8,9+10)
  - Significant relation between EFI and non-ART pregnancy?
  - Assessment of qualitative performance (predictive accuracy, discriminative ability)
    - mean squared error (MSE, 'Brier score')
    - proportion of variation explained by the model (R^2)
    - area under the receiving-operating curve (AUC), the latter resulting from values for sensitivity and specificity and also known as the index of concordance (C-index).

Tomassetti et al, Hum Reprod 2013

Validation of the EFI

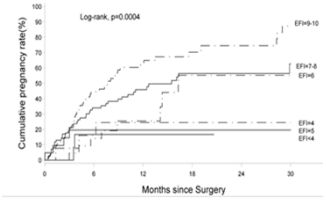


Tomassetti et al, Hum Reprod 2013

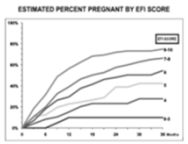
Validation of the EFI

Cumulative non-ART pregnancy rate (K-M) per EFI subgroup

Tomassetti et al, Hum Reprod 2013



Clearly significant relationship between EFI and time to non-ART pregnancy (p=0.0004)



Adamson and Pasta, 2010

Moderate performance for prediction

- **Small decrease in Brier score**
- **Low estimates for R^2 (range from 7% to 13%)**
- **Low C* 0.63 (0.5 - 1.0 : random – perfect)**

Validation of the EFI

- **Not only a significant relationship, but also:**
  - Linear relationship between EFI en non-ART pregn (Cox regression)
  - Increase of 1 point in EFI results in a relative increase of non-ART pregnancy rate with 31%
- **The 'least function score' (LF) is the most important contributor to the total score:**
  - More than the 'endometriosis'-scores
  - EFI – LF: still significante contribution of the other factors (p=0.016
- **ART-treatment can be defered or advised based on an objective judgment - not on mere rAFS staging**
  - Reassurance in good prognosis patients – avoiding waisting time in poor prognosis patients
  - Confirmation of current 'intuitive practice' at LUFc

Tomassetti et al, Hum Reprod 2013

Validation of the EFI

- Other validations
  - Wei et al, 2011:
    - Retrospective analysis, n=350, K-M
    - Confirming sign relation EFI and pregnancy rate (detail?°
  - Yacoub et al, 2011 (abstract WES Montpellier):
    - Retrospective analyse
    - Relation EFI and pregn rates with IUI orIVF
    - no significant relationship between rAFS and PR

FIGURE 2. Cumulative live birth rate by Endometriosis Fertility Index (EFI) Score [or revised American Fertility Society (rAFS stage)] at specific times after laparoscopy. (a) By rAFS stage. (b) By EFI. Note that grouping of EFI score used by Yacoub *et al.* [17] in their comparison with rAFS stage is different than the actual published EFI grouping of scores published by Adamson and Pasta [15••]. (Adapted from [17]).

A FEW CASES

Casus 1

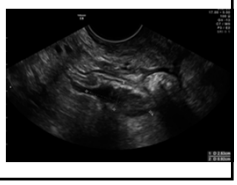
- 30 y
- A0P1G1
  - IVF-pregnancy (2de cycle – other hospital), normal pregnancy and partus
  - Previously 4 failed IUI in nat cycle for 'unexplained' infertiliteit (normal TVUSS, hysteroscopy and HSG; normal spermiogram) 12 mths

Casus 1

- Problem:
  - Secondary subfertility 1 year
  - Severe endometriosis symptoms
    - Dysmenorree grade 3
    - Dyschezia during menses with cramping +++
    - Painful and frequent micturition pre/permenstrual
    - No dyspareunie
    - Fatigue

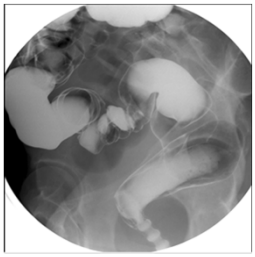
Casus 1

- Clinical examination: nodule left uterosacral ligament without invasion of the vaginal mucosa
- TVUSS:
  - Bladder nodule
  - Nodule posterior sigmoid
  - Several smaller nodules rectovag septum



Casus 1

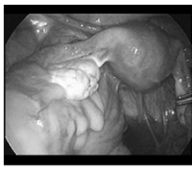
- Barium enema: transmural endometriosis of the proximal sigmoid, distance 10cm

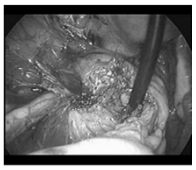


- IV urography: normal

Casus 1

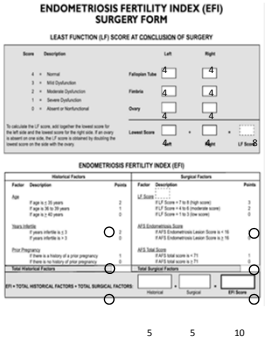
- Surgery 1/2013:
  - CO2-laser laparoscopic resection of all endometriotic nodules (ureterstents, hysteroscopie)
  - lapsc sigmoidresection with transanal extraction
  - rAFS IV (50 punten)





Casus 1

- EFI 10/10
  - Pregn chance without IVF:
    - 62,5% at 12m
- Suggested management:
  - 6-12m expectant (despite history IVF)


ENDOMETRIOSIS FERTILITY INDEX (EFI)
SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description	Left	Right
4	= Normal	Fallopian Tube: 4	4
3	= Mild Dysfunction		
2	= Moderate Dysfunction	Fimbria: 4	4
1	= Severe Dysfunction		
0	= Absent or Nonfunctional	Ovary: 4	4
		Lowest Score: 4 (Left) × 4 (Right)	LF Score: 8

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		FLF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		FLF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		FLF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical 5 + Surgical 5 = EFI Score 10

Casus 1

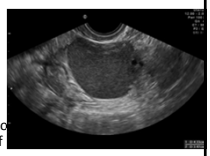
- Stop COC 4/2013
- Spontaneous pregnancy 11/2014

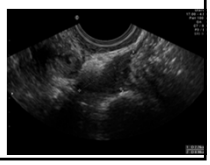
Casus 2

- 27 jaar
- A0P0G0
- Primary infertility 1 year
- Endometriosis symptoms:
  - Dysmenorree grade 1-2
  - Dyspareunie (deep)
  - Dyschezia and painfum micturition when menses
  - Occasionally diarrhea

Casus 2

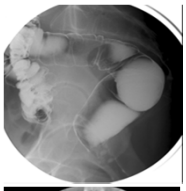
- Clinical examination:
  - Central rectovag septum nodule 2cm
- TVUS:
  - Subserosal myoma fundal 40x24x40mm
  - Endometrioma left 43x35x38mm, midly dilated left tube
  - Obliterated douglas, large nodule on the anterior recto sigmoidal limit (with disruption of the full thickness of the muscularis) of 23x10mm.
  - Second nodule in the rectovaginal septum of 3.3x1.7 mm and retrocervical nodule (in de douglasholte) of 6.1x5.1

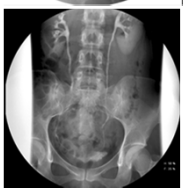




Casus 2

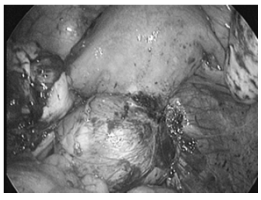
- Barium enema: transmural invasie of the rectosigmoid colon
- IV urography: peri-ureteral endometriose: medial displacement of the left pelvic ureter



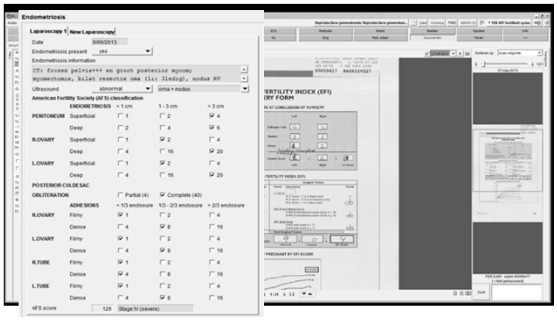


Casus 2

- Surgery:
  - Stent, hysc
  - CO2-laserlaparoscopic resection of endometriotic nodules and cyst and myomectomy
  - Laparoscopic anteriorresection with transrectal extraction and side to end reconstruction.



Casus 2



Casus 2

- EFI 4/10:
  - Chance non-ART pregn at 12m: max 25%
  - Cave recurrence of endometrioma
  - (sperm sample of partner is normal)
- Beleid: low threshold for IVF, ev after short period of expectant management
  - Patient preferred first 6m expectant mx

Casus 2

- After 6m : not pregnant
  - IVF-procedure started

The promise of IVM for the treatment of infertility in patients with PCOS

Michel De Vos, MD, PhD
Medical Co-director
Centre for Reproductive Medicine, UZ Brussel, Belgium

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Disclosure

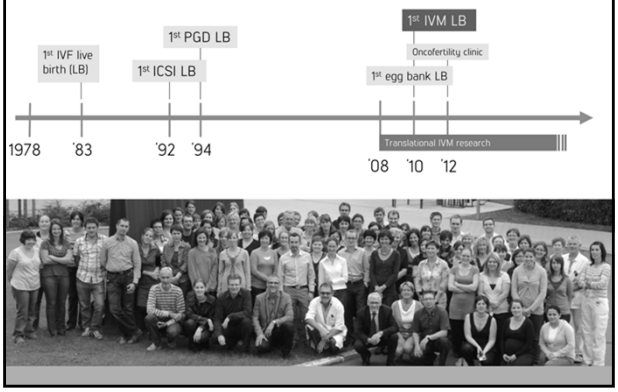
- I have no commercial and/or financial relationships with any manufacturer of pharmaceuticals, laboratory supplies and/or medical devices.

Learning objectives

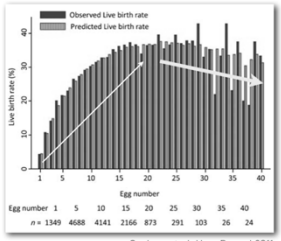
At the end of this lecture attendees should be able to

- Appreciate the current status of IVM in human ART
- Understand the main clinical and laboratory aspects of an IVM clinical program
  - clinical approach
  - clinical outcomes and troubleshooting
- Apprehend the new developments on the horizon

Centre for Reproductive Medicine, UZ Brussel, B



"Predicted high responders (to gonadotrophins in conventional ART) have better outcomes"



Sunkara et al. Hum Reprod 2011
over 400.000 IVF cycles

"Superior treatment outcome in patients with AMH > 5 ng/dL"

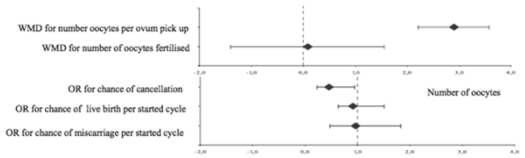
Serum AMH

- is correlated to live birth rate after ART (through its correlation with the number of oocytes after ovarian stimulation)
- is not correlated to oocyte quality

Nelson et al. Hum Reprod 2012

The more eggs the better?

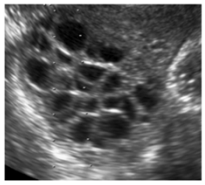
Do PCOS patients really have better outcomes after c-ART?



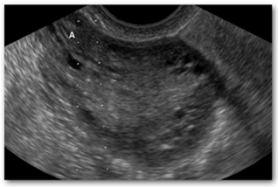
Heijnen et al. Hum Reprod Update 2006
Meta-analysis
9 matched control studies (GnRH agonist protocol)

PCOS and control patients achieve similar pregnancy and live birth rates per cycle at the expense of higher cancellation rates and higher risk of OHSS

ART in "difficult" PCOS patients is cumbersome

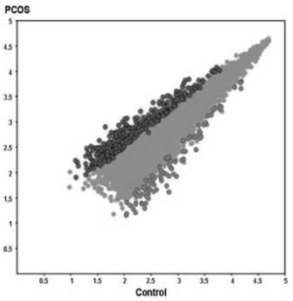


PCOS, normoandrogenaemic, AMH 10 ng/dL



PCOS, hyperandrogenaemic, AMH 16 ng/dL

Inferior quality of oocytes from PCOS women



Meiotic cell cycle genes are differently expressed in oocytes from PCOS women compared to controls

Wood et al. JCEM 2007

Qiao and Feng, Hum Reprod Update 2011
Harris et al. Hum Reprod 2010

Altered endometrium transcriptome in obese PCOS patients

Number of upregulated and downregulated genes revealed by comparisons using nonparametric (Rank product) and parametric methods (SAM).

No. of genes	Rank-product			SAM		
Comparison	Up	Down	Total	Up	Down	Total
B-A	182	31	213	127	15	142
C-A	187	15	202	80	3	83
C-B	30	3	33	0	0	0
D-C	331	522	853	289	460	749
E-C	113	229	342	18	127	145
D-E	22	57	79	0	0	0

Note: A = control group, normal weight, fertile, ovulatory women; B = obese, fertile, ovulatory women; C = obese, infertile, ovulatory women; D = obese, infertile, anovulatory women undergoing ovarian stimulation; E = obese, infertile, ovulatory women undergoing ovarian stimulation.

Bellver. Obesity, polycystic ovary, and endometrium. Fertil Steril 2011.

Endometrium quality in stimulated PCOS patients is compromised

Current ART practice for predicted high responders to gonadotrophin stimulation

GnRH antagonist protocol
GnRH agonist trigger

- FRESH embryo transfer + modified luteal support (if > 14 follicles ≥11 mm on the day of trigger)

RISK of OHSS	LOW (4.4%)
RISK of SEVERE OHSS	VERY LOW (0.7%)
CLINICAL PREGNANCY RATE	41,8% per started cycle (Iliodromiti et al. Human Reprod 2013) (n=275)

Current ART practice for predicted high responders to gonadotrophin stimulation

GnRH antagonist protocol
GnRH agonist trigger

- Elective VITRIFICATION and warmed embryo transfer in a natural or artificial cycle (if > 25 follicles ≥11 mm on the day of trigger)

Treatment segmentation
"OHSS-free" clinic

Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and "freeze-all" approach in GnRH antagonist protocol

Human Mousavi Fatemi, M.D., Ph.D.,[a] Biljana Popovic-Todorovic, M.D., Ph.D.,[a] Peter Humaidan, M.D., D.M.Sc.,[b] Shahar Kol, M.D., Ph.D.,[c] Manish Banker, M.D.,[d] Paul Devroey, M.D., Ph.D.,[a] and Juan Antonio Garcia-Velasco, M.D., Ph.D.[a]

Fatemi et al. F&S 2014

Current ART practice for predicted high responders to gonadotrophin stimulation

	CONVENTIONAL ART • GnRH antagonist protocol • trigger with GnRH agonist • modified luteal support	IVM • minimal ovarian stimulation or none • trigger with hCG or none
RISK of OHSS	LOW	NEVER REPORTED
RISK of SEVERE OHSS	VERY LOW	
CLINICAL PREGNANCY RATE	More than 40%	VARIABLE OUTCOMES 0-50% Publication bias LESS EFFICIENT

Efficiency gap

IVM derived embryos have a lower implantation potential

Current IVM is not physiological

Oocyte quality is lower (loss of cumulus cell support, final maturation signaling pathways are artificial)

Barrett and Albertini. Biol Reprod 2007

Endometrium receptivity may be compromised

Requena et al., Hum Reprod 2005

Children's health data are still limited -> experimental?

Cha et al., Fertil Steril 2005; Söderström-Anttila, Hum Reprod 2006; Buckett et al., Obstet Gynecol 2007

IVM versus conventional ART in PCO

	IVF group (n = 97)	IVM group (n = 97)	*P* value
Cycle			
Follicles retrieved	22.2 ± 9.0	35.3 ± 18.6	<.0001
Eggs retrieved	17.2 ± 9.9	15.8 ± 7.2	NS
Oocytes/follicle	75.7	48.8	<.0001
Maturation rate	–	65.01	–
Mature oocytes obtained[a]	12.3 ± 6.2	11.2 ± 7.0	NS
Fertilization rate	61.5	62.9	NS
Cleaving embryos	9.6 ± 5.8	6.4 ± 4.8	<.0001
Embryos transferred	1.7 ± 0.6	1.9 ± 0.4	.0043
Day 2	8	13	NS
Day 3	58	80	.0008
Day 5	24	0	<.0001
No transfer	7[c]	4[d]	NS
Embryos frozen	2.6 ± 3.2	1.4 ± 2.7	.0058
Outcome			
Biochemical pregnancy	63.9 (62)	28.9 (28)	<.0001
Clinical pregnancy[b]	50.5 (49)	19.6 (19)	<.0001
Miscarriage	12.2 (6)	15.8 (3)	NS
Live birth rate	44.3 (43)	16.5 (16)	<.0001
Implantation rate	39.4	12.9	<.0001
Twins	25.6 (11)	25 (4)	NS

Note: Values are presented as mean ± SD, percent, or percent (n). NS = not significant.
[a] Oocyte maturation is not assessed on IVF, so we compared 38 ICSI cycles (metaphase II = 469) with 97 IVM cycles (metaphase II = 1,087).
[b] Clinical pregnancy = fetal heart activity at ultrasonographic scan 8 weeks' gestation.
[c] FIV = 4 freeze-all embryo for risk of OHSS + 3 failed fertilization.
[d] MIV = 3 failed fertilization + 1 freeze-all embryo for significant bleeding after oocyte retrieval.

Gremeau. IVM or IVF for women with PCO. Fertil Steril 2012.

EFFICIENCY GAP

Defining the incentive of mild approaches in ART

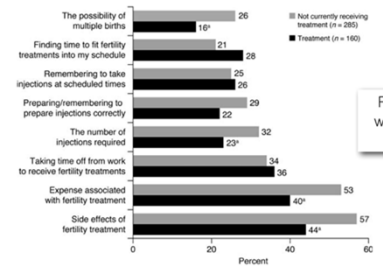
Novel trend in human ART to increase SAFETY and PATIENT-FRIENDLINESS

Devroey et al., Hum Reprod 2011

Trend towards mild ovarian stimulation in IVF with the emphasis on recovering fewer eggs than previously deemed optimal

Fauser et al., Hum Reprod 2010

Towards a more patient-friendly approach in ART



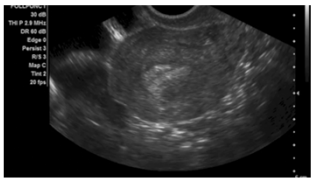
Feelings and behaviors of women in Europe resulting from infertility

Domar et al. Hum Reprod 2012

Why consider IVM?

IVM as an emerging tool in fertility preservation

Huang et al. Am J Surg 2010. Shalom-Paz et al. RBM Online 2010



Advanced stage breast cancer, luteal phase oocyte retrieval
23 COC retrieved. 12 MII oocytes vitrified

OTC for leukaemia, ex-vivo oocyte retrieval
40 COC retrieved. 16 MII oocytes vitrified

Rescue IVM: not recommended

Immature oocytes that have failed to respond to the gonadotropin ovulation stimulus in standard IVF/ICSI cycles are ABNORMAL

Increased aneuploidy rate and abnormal gene expression pattern

Table II. Fold change differences in gene expression for the majority of *in vivo* (MII) and *in vitro* matured (IVM) oocyte microarrays (*$P < 0.05$).

Trend	Gene expression	Significantly* different	>2-fold	>5-fold	>10-fold	>25-fold	>50-fold
IVM>MII	Genes	2627	2348	1025	162	7	3
	Probes	3776	3166	1280	197	12	3
IVM< MII	Genes	139	42	15	3	0	0
	Probes	450	84	23	6	0	0

Jones et al., Hum Reprod 2008

IVM egg collection involves:

- Multiple ovarian punctures since the single-channel aspiration needle tends to block frequently when passing through the dense ovarian stroma and follicular flushing is not performed.
- The collection also takes, on average, longer than an IVF oocyte retrieval. ?
- Consequently, the procedure is likely to be more painful than a routine IVF oocyte collection. ?
- The synchrony between endometrial and embryonic development in fresh IVM ET cycles is undoubtedly not ideal, it would appear a superior strategy to freeze-thaw all embryos.

Child et al., Fertil Steril 2001

IVM OPU complication rates in an experienced centre

Complication	IVM (n = 188)	IVF (n = 188)
None	183 (97.3)	177 (94.1)
Ovarian bleeding	1 (0.5)	2 (1.1)
Vaginal bleeding	1 (0.5)	2 (1.1)
Fever	1 (0.5)	0 (0)
Endometrioma perforation	1 (0.5)	1 (0.5)
Ovarian abscess	0 (0)	1 (0.5)
Severe postoperative pain	1 (0.5)	5 (2.7)

Note: Values are number (percentage). Statistics not applicable.

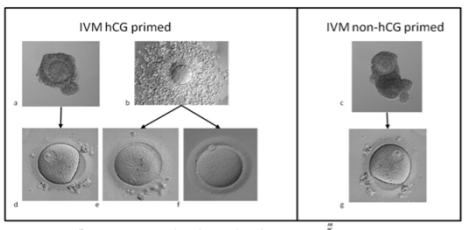
Seyhan. IVM OPU complications. Fertil Steril 2014.

Characteristic	IVM (n = 188)	IVF (n = 188)	*P* value
Age, y (SD)	32.8 (5.3)	35.7 (4.6)	<.01
BMI in kg/m^2 (SD)[a]	23.5 (5.1)	24.6 (5.3)	.08
Duration in minutes (25th–75th percentile)	22 (10–30)	15 (10–20)	<.01
Oocytes collected (SD)	11.7 (9.1)	11.4 (7.2)	.74

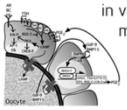
On average, the procedure takes longer

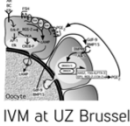
Complication rates are not increased

Two disctinct IVM systems



in vivo + in vitro maturation

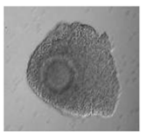




IVM at UZ Brussel

hCG trigger in "IVM"?

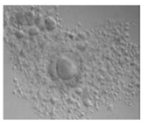
compact cumulus



GV

PR 23,3%

expanded cumulus

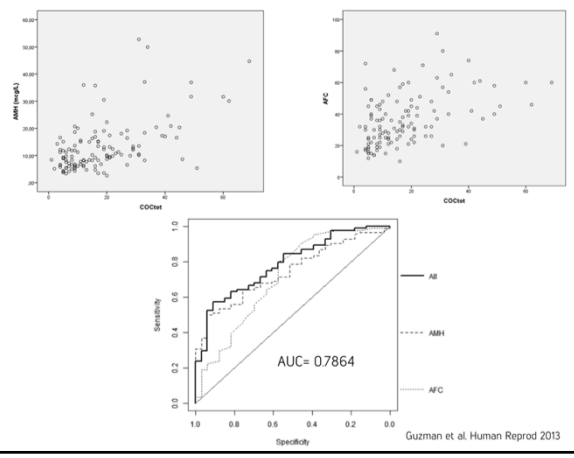


GV
MI
MII

PR 40%

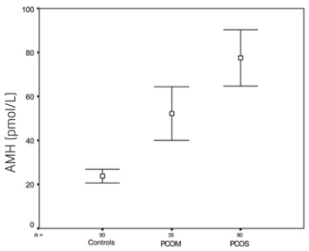
Son et al. RBM Online 2008

In vivo + in vitro maturation



Guzman et al. Human Reprod 2013

Trying to define the target population for IVM



controls PCOM PCOS

~ 20% ~ 7%

Homburg et al. Hum Reprod 2013

Selection of patients suitable for IVM

Table I Cumulative clinical outcome per initiated cycle.

	Overall	Less than eight COC	At least eight COC	*P*-value
Patients	124	45	79	
Ongoing pregnancy rate after fresh ET	10% (8 out of 83)	11% (3 out of 27)	9% (5 out of 56)	0.711
Cumulative ongoing pregnancy rate (after fresh ET + FET)	23.4% (29 out of 124)	11% (5 out of 45)	30.4% (24 out of 79)	0.01
Mean number of embryos transferred (fresh ET)	1.17 ± 0.37	1.11 ± 0.32	1.20 ± 0.40	0.334
Mean number of embryos transferred (FET)	1.48 ± 0.46	1.50 ± 0.58	1.48 ± 0.45	0.952

ET, embryo transfer; FET, frozen embryo transfer.

Guzman et al. Hum Reprod 2013

Dissociate embryo generation and embryo transfer

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

A "freeze-all" embryo strategy after in vitro maturation: a novel approach in women with polycystic ovary syndrome?

Carolina Ortega-Hrepich, M.D.,[a] Dominic Stoop, M.D., Ph.D.,[a] Luis Guzmán, M.Sc.,[a] Lisbet Van Landuyt, M.Sc.,[a] Herman Tournaye, M.D., Ph.D.,[a] Johan Smitz, M.D., Ph.D.,[b] and Michel De Vos, M.D., Ph.D.[a]

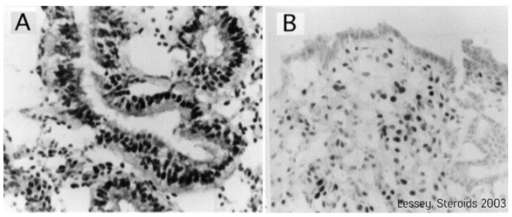
[a] Center for Reproductive Medicine and [b] Laboratory of Clinical Chemistry and Radioimmunology, Universitair Ziekenhuis Brussel, Brussels, Belgium

Clinical outcome: frozen embryo transfer cycles, % (n).

	All	SET	DET
No. of patients	78	31	50
No. of started FET	114	NA	NA
No. of warming cycles with ET	105	39	66
No. of embryos transferred	171	39	132
No. of cancelled cycles, n (%)	9 (7.9)	NA	NA
Ongoing pregnancy /patient	24.4 (19/78)	16.1 (5/31)	28.0 (14/50)
Miscarriage rate/ET	32.1 (9/28)	37.5 (3/8)	30.0 (6/20)

Ortega-Hrepich et al., F&S 2013

How to obtain a receptive endometrium in IVM cycles?



Lessey, Steroids 2003

proliferative endometrium mid-secretory endometrium

The establishment of normal endometrial receptivity appears to be tightly associated with the down-regulation of epithelial PR.

Histologic delay, consistent with LPD, is associated with a failure of PR down-regulation.

Lessey et al., Fertil Steril 1996

Troubleshooting endometrium

PROBLEM:

Insufficient priming with estradiol?
Delayed downregulation of PR expression due to insufficient progesterone levels?
Inappropriate timing of P4 supplementation?

SOLUTION:

Effect of hCG on endometrium?
Modify estrogen/progesterone supplementation?
Delay embryo transfer?

Promising results of IVM treatment

Results of the in vitro maturation protocol in women with polycystic ovaries (PCO) or polycystic ovary syndrome (PCOS).

Parameter	PCO	PCOS	Total
Cycles	19	47	66
Oocytes collected	167	677	844
MII oocytes after IVM	115 (68.9%)	473 (69.9%)	588 (69.7%)
Normally fertilized	85 (73.9%)	335 (70.8%)	420 (71.4%)
Blastocysts (day 5/6)	35 (41.1%)	140 (41.8%)	175 (41.7%)
Embryo transfers	18	44	62
Clinical pregnancies	8 (42.1%/EC; 44.4%/ET)	21 (44.7%/EC; 47.7%/ET)	29 (43.9%/EC; 46.7%/ET)
Live births	8 (42.1%/EC; 44.4%/ET)	20* (42.6%/EC; 45.5%/ET)	28* (42.4%/EC; 45.2%/ET)

Junk et al., F&S 2012

- 24 – 26 h IVM (SAGE + patient serum)
- FSH priming, no hCG trigger
- follicles 12 mm
- fresh single blastocyst transfer

- LBR/cycle 42,4%

Polycystic ovary after IVM

Table 2 Endocrine profile after oocyte retrieval (OR) for IVM in PCOS

	Basal	OR day (All values compared to basal values)	5 days after OR (All values compared to OR values)	2 weeks after OR (All values compared to OR values)
AMH (μg/L)	8.9 ± 4.0	7.5 ± 3.2*	6.3 ± 3.2*	7.6 ± 3.6^{NS}
TT (nmol/L)	0.36 ± 0.13	0.48 ± 0.21*	0.28 ± 0.12**	0.22 ± 0.1*
FTc (pmol/L)	5.0 ± 3.6	5.3 ± 2.9^{NS}	2.9 ± 1.8**	2.7 ± 1.5*
SHBG (nmol/L)	74.6 ± 59.1	85.1 ± 48.3^{NS}	99.4 ± 57.3*	81.6 ± 54.4^{NS}
LH (IU/L)	7.9 ± 4.4	10.2 ± 7.8^{NS}	5.8 ± 4.1*	3.7 ± 3.0*

Values represent mean and SD.
AMH Antimüllerian hormone, *TT* total testosterone, *SHBG* sex hormone-binding globulin, *FTc* calculated free testosterone, *LH* Luteinizing hormone, *FSH* Follicle-stimulating hormone. *P < 0.05; **P < 0.001; *NS* not statistically different.

Ortega-Hrepich et al., RBE 2014

IVM is not just a method to reduce OHSS risk

IVM neither represents an alternative nor a substitute for IVF, but rather a useful additional tool, in line with the current positive attitude toward simpler, more economical, safer and less wasteful IVF procedures (Fadini, 2009)

Study of the control of meiotic progression and the modulation of endometrial receptivity will provide crucial hints for the development of more efficient IVM systems.

References

1. Jones GM, Cram DS, Song B, Magli MC, Gianaroli L, Lacham-Kaplan O, et al. Gene expression profiling of human oocytes following in vivo or in vitro maturation. Hum Reprod. 2008.
2. Child TJ, Abdul-Jalil AK, Gulekli B, Tan SL. In vitro maturation and fertilization of oocytes from unstimulated normal ovaries, polycystic ovaries, and women with polycystic ovary syndrome. Fertil Steril. 2001.
3. Gremeau A-S, Andreadis N, Fatum M, Craig J, Turner K, Mcveigh E, et al. In vitro maturation or in vitro fertilization for women with polycystic ovaries? A case–control study of 194 treatment cycles. Fertil Steril. 2012.
4. Seyhan A, Ata B, Son W-Y, Dahan MH, Tan SL. Comparison of complication rates and pain scores after transvaginal ultrasound-guided oocyte pickup procedures for in vitro maturation and in vitro fertilization cycles. Fertil Steril. 2014.
5. Son W-Y, Chung J-T, Demirtas E, Holzer H, Sylvestre C, Buckett W, et al. Comparison of in-vitro maturation cycles with and without in-vivo matured oocytes retrieved. Reprod Biomed Online. 2008.
6. Guzman L, Ortega-Hrepich C, Polyzos NP, Anckaert E, Verheyen G, Coucke W, et al. A prediction model to select PCOS patients suitable for IVM treatment based on anti-Mullerian hormone and antral follicle count. Human Reproduction. 2013.
7. Homburg R, Ray A, Bhide P, Gudi A, Shah A, Timms P, et al. The relationship of serum anti-Mullerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study. Human Reproduction. 2013.
8. Ortega-Hrepich C, Stoop D, Guzman L, Van Landuyt L, Tournaye H, Smitz J, et al. A "freeze-all" embryo strategy after in vitro maturation: a novel approach in women with polycystic ovary syndrome? Fertil Steril. 2013.
9. Junk SM, Yeap D. Improved implantation and ongoing pregnancy rates after single-embryo transfer with an optimized protocol for in vitro oocyte maturation in women with polycystic ovaries and polycystic ovary syndrome. Fertil Steril. 2012.
10. Ortega-Hrepich C, Polyzos NP, Anckaert E, Guzman L, Tournaye H, Smitz J, et al. The effect of ovarian puncture on the endocrine profile of PCOS patients who undergo IVM. Reprod Biol Endocrinol. 2014.

Acknowledgements

- Centre for Reproductive Medicine, UZ Brussel, VUB
  - Michel De Vos
  - Samuel Ribero Dos Santos
  - study nurses, embryologists
- Laboratory of Follicular Biology, UZ Brussel, VUB
  - Johan Smitz
  - Ingrid Segers
  - Ellen Anckaert
  - Sergio Romero
  - Flor Sanchez
- University of New South Wales, Sydney, Australia
  - Rob Gilchrist
- University of Adelaide, Adelaide, Australia
  - Jeremy Thompson

BESINS HEALTHCARE
Innovating for Well-being

COOK® MEDICAL

Counselling for genetic disorders

Catherine King, RGN, MSc
Genetic Nurse Counsellor

No commercial interest or conflict of interest to declare

Learning Objectives

Increase awareness of:

* The Clinical Genetics Service and the role of the genetic counsellors
* Genetic disorders for which couples may seek access to assisted reproduction services
* Genetic disorders identified through fertility investigations, and the implications for the couple and wider family

Aim of Clinical Genetics Service

"The aim of the Clinical Genetic Department is to provide genetic information, diagnosis, counselling, management and support to patients and families with genetic disorders"

Clinical Genetics Team:

- Picture here

*Consultants in Clinical Genetics

*Specialist Registrars

*Genetic Counsellors

*Administrative staff

*Work closely with genetics laboratory staff

Role of the Genetic Counsellor

- To work alongside Consultant colleagues to provide genetic services throughout region
- First point of contact for families
- Historically, supportive role when children referred for diagnosis
- Role has developed with increasing levels of genetic knowledge and availability of genetic testing, to include autonomous caseloads

Counsellor caseload

* Pre-clinic preparation of families attending Consultant Clinics and ongoing psychosocial support as required (paediatric and adult)
* Counselling for 'predictive' testing for adult onset neurological disorders / Cancer genes
* Autonomous caseload including carrier testing/risk assessment for families e.g with chromosome translocations, Cystic Fibrosis
* Includes couples referred by assisted conception services following investigations for infertility, or donor screening

Genetic Counsellor Registration process

* Recognised need for regulatory process, given increasing autonomy of workload
* Eligibility: Graduate Nurse or Midwife with:
  - 2 years post-registration experience
  - Counselling skills training (90 hours minimum)
  - Genetics course (30 hours minimum)

  MSc in Genetic Counselling
* Minimum of 2 years clinical practice as a Genetic Counsellor
* First Genetic Counsellors registered in 2002
* Similar registration process currently being developed in Europe, first cohort expected to register in 2014

For many families, whatever the initial reason for referral, counselling issues will include recurrence risks and future reproductive choices

* Couple whose fertility investigations / CVS test has shown chromosome rearrangement inherited from a parent
* Child diagnosed with a single gene disorder inherited from a parent (X-linked or Dominant), or caused by inheriting gene changes from both parents (Recessive)
* Adults requesting predictive testing for late onset neurological disorder (e.g. Huntington's Disease) to inform reproductive choices
* Includes index case and wider family

Reproductive Options

* As more genes identified, more couples can be offered reproductive choices

* PND - Amniocentesis since 1966
  - Chorionic Villus Sampling since 1978
* PND not appropriate for many couples
* Alternatives considered:
  - Adoption
  - Donor gametes
  - Pre-implantation genetic diagnosis (PGD)

Preimplantation Genetic Diagnosis

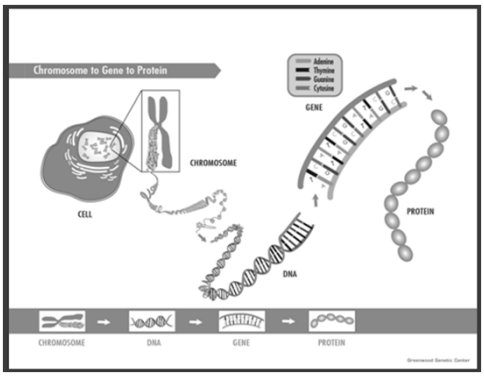
* Combines IVF and Genetic Procedures, testing embryos prior to implantation
* In the UK, PGD requires licence for HFEA for each condition
* Currently funding for up to 3 cycles for couples meeting criteria

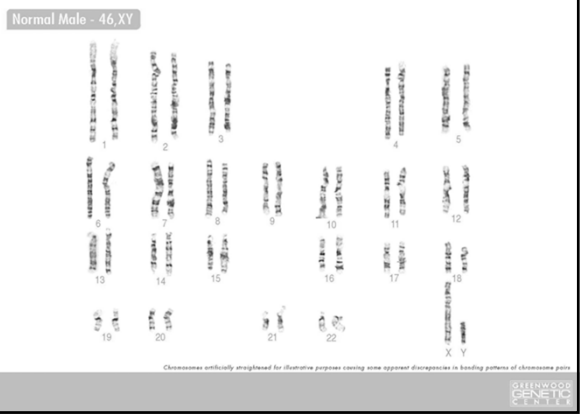
What is a genetic condition?

* Any condition which is caused by an alteration in a gene or chromosome
* Genetic does not always mean inherited
* 1 in 18 (5.5%) will have developed a genetic disorder by the age of 25 (www.geneticalliance.org.uk)

Causes of genetic conditions

* Chromosomal e.g. Down syndrome
* Gene mutation e.g. cystic fibrosis
* Mitochondrial mutation e.g. Leber's optic atrophy
* Multi-factorial (genetic and environmental) e.g. neural tube defect





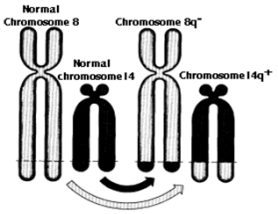
Chromosomal disorders

* Sex chromosome aneuploidy may present with infertility
* Turner Syndrome -45X Klinefelter Syndrome – 47,XXY

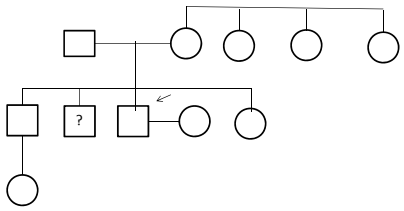
Picture here Picture here

Translocations

* Can involve any combination of chromosomes
* Impact dependent on specific regions involved
* Increased risk of miscarriage
* Potential risk of live born with multiple abnormalities
* Can interfere with fertility

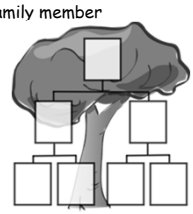


X;autosome translocation:
Importance of family understanding and communication

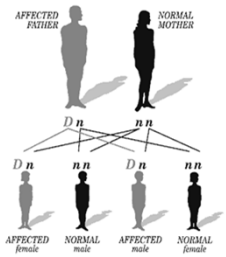


Single gene mutations

* Follow Mendelian patterns of inheritance
* May be passed on through generations
* Important to establish pattern of inheritance to determine implications for couple and/ or other family member
* Family tree (pedigree) important



Autosomal Dominant Inheritance

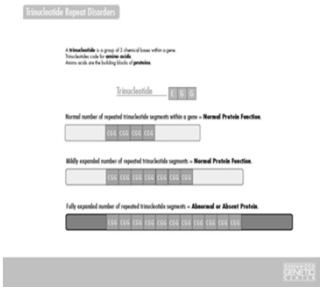


* Multiple generations affected
* Males and females affected equally
* Male to male transmission occurs
* Each child of an affected person has a 50% risk of inheriting the condition
* Variable expression, non-penetrance and anticipation

www.geneticalliance.org.uk

Anticipation:

* Expansion of a triplet repeat sequence within a gene
* Associated with increased severity of disease in successive generations

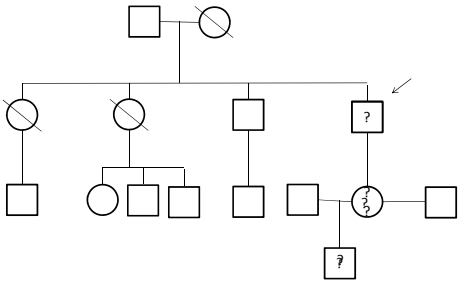


Myotonic Dystrophy

* DMPK gene on chromosome 19
* Progressive multisystem disorder
  - Muscle wasting and weakness
  - Myotonia
  - Cataracts
  - Cardiac
  - Diabetes
* Variable presentation:
  - Mild – cataracts only in adulthood
  - Classic - onset of symptoms age 20-30 yrs
  - Congenital – severe respiratory insufficiency
* Maternal Anticipation

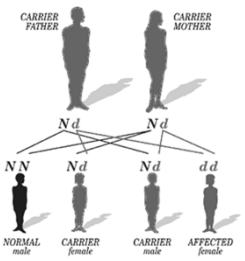
- Picture here

Myotonic Dystrophy – avoidance of high risk pregnancy



Autosomal Recessive Inheritance

* Greatest recurrence risk is for sibs of affected child
* Males and females affected equally
* If parents both carry a recessive gene each child has 25% chance of being affected
* Ethnic background and consanguinity are relevant

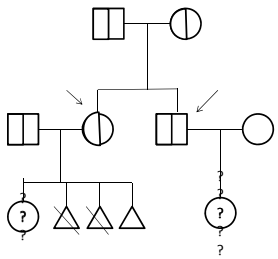


www.geneticalliance.org.uk

Cystic Fibrosis

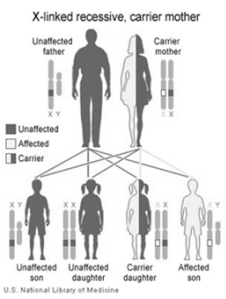
* Most common inherited condition in Western Europe (@ 1 in 2000)
* Associated with infertility in males, due to CBAVD
* Known Affecteds referred for Sperm Retrieval
* Carriers identified through fertility investigations (azoospermia) or donor screening

Cystic Fibrosis –
Impact of genetic investigations for wider family



X-linked inheritance

* Caused by a gene alteration on the X chromosome
* Mainly males affected; women can be carriers
* Carrier females have a 25% chance of having an affected boy.
* Do NOT see male to male transmission
* All daughters of affected males will be carriers

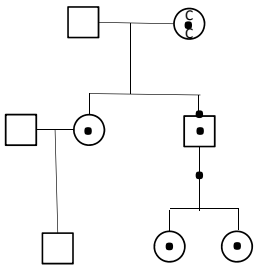


Fragile X Syndrome

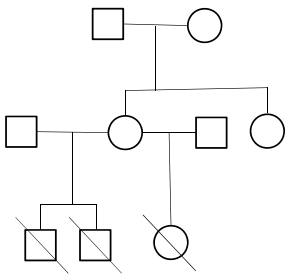
* Most common cause of severe learning difficulties in males
* Females can be affected as well
* Triplet repeat expansion in FMR1 gene
* Premutation carriers and 'Normal Transmitting Males'
* Associated with POF in carrier females

- Picture here

Fragile X Syndrome – Implications for family



Complex Case - Importance of genetic testing



Issues working with families

* Confidentiality
* Family Communication:
  - Non-disclosure
  - Myths, secrets, conflict
* Ethical Dilemmas
* Complexity of Information
* Privileged to be working as a genetic counsellor

- Picture here

Useful sources of information

* Career in Genetic Counselling:

  www.gcrb.org.uk
  www.agnc.org.uk
  www.eshg.org

* Information on genetic disorders:

  www.orpha.net
  www.ncbi.nlm.nih.gov/boks/NBK1116/ (Gene Reviews)
  www.geneticalliance.org.uk

Microarray tools for PGD: an introduction

Prof Martine De Rycke
Medical Genetics, UZ Brussel, Laarbeeklaan 101, 1090 Brussel
martine.derycke@uzbrussel.be

Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel
Centrum voor Medische Genetica
Centrum voor Reproductieve Geneeskunde

Disclosure

Prof Martine De Rycke
Medical Genetics, UZ Brussel, Laarbeeklaan 101, 1090 Brussel
martine.derycke@uzbrussel.be

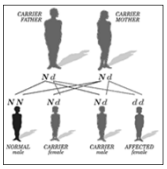
The author reports no conflict of interest.

Objectives

- basics of PGD and PGS
- standard genetic testing: FISH and PCR
- whole genome amplification
- array CGH for chromosomal imbalances
- SNP array for monogenic disorders

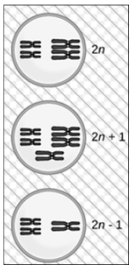
Preimplantation Genetic Diagnosis

- an alternative to prenatal diagnosis and TOP
- involves genetic testing of cells biopsied from *in vitro* obtained oocytes and/or *in vitro* fertilised embryos and selective transfer of unaffected embryos
- for couples at ***high*** risk of transmitting a genetic condition to their children



Preimplantation Genetic Screening

- PGS or aneuploidy screening involves selection of euploid embryos to improve IVF results and reduce miscarriage rates
- for specific IVF patients groups at ***low*** risk (advanced maternal age, recurrent IVF failure or repeated miscarriages)



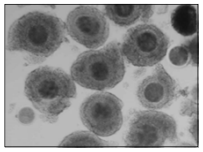
PGD workflow in daily practice

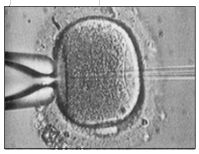
- multidisciplinary team
  - collaboration between IVF and diagnostic genetics unit: in-house and/or transport PGD cycles
- Intake of PGD request at the IVF/genetics unit
  - counselling and informed consent
- pre-PGD workup in the genetics lab
  - development of single-cell test
- PGD clinical cycle
- follow-up
  - of cycles, pregnancies and children

PGD clinical cycle

oocyte collection
after hormonal
stimulation (day 0)

IVF with
Intracytoplasmic sperm
injection (day 0)

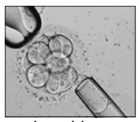




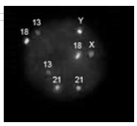
Day 0

Centrum voor Medische Genetica

PGD clinical cycle: standard genetic testing



embryo biopsy
with laser (day 3)



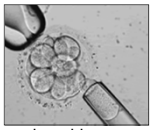
FISH

embryo transfer
(day 5)

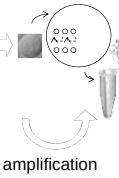
interphase FISH: for sex determination (X-linked disorders) and chromosomal aberrations (numerical and structural (translocations)) was also used for PGS

Centrum voor Medische Genetica

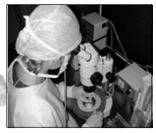
PGD clinical cycle: standard genetic testing



embryo biopsy
with laser (day 3)



amplification



embryo transfer
(day 5)

multiplex PCR of linked STR markers w/wo mutation(s): for monogenic disorders and HLA typing

Centrum voor Medische Genetica

PGD/PGS: standard genetic tests

request for mutation/gene/locus 1 => or request for translocation 1 =>	develop single cell PCR 1 test specific FISH probes 1
request for mutation/gene/locus n => or request for translocation n =>	develop single cell PCR n test specific FISH probes n

PGD: customised protocols: optimisation and validation at the single cell level: has to be repeated each time => pre-PGD workup is labour-intensive and time-consuming and yields high costs

PGS: RCTs: no benefit for PGS with FISH at cleavage stage (Checa et al., 2009) => biological and technical reasons => switch to array comparative genomic hybridisation (array CGH)

Centrum voor Medische Genetica

10 titel 18-5-2014

PGD/PGS: emerging array tests

emerging array platforms are genome-wide and allow standardisation and automation

universal single cell WGA
↓
several µg of DNA
↓
multiple downstream analyses

optimisation and validation of single cell whole genome amplification (WGA): only 1 time!

=> pre-PGD workup labour, time and costs are reduced

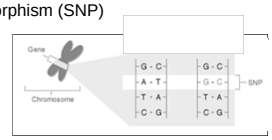
Centrum voor Medische Genetica

11 titel 18-5-2014

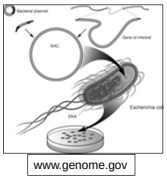
Intermezzo: scales of DNA

1 bp (basepair): may differ between individuals =>
single nucleotide polymorphism (SNP)

100.000 bp = 100 kb
= size of a typical gene



200 kb = size of a BAC clone
(bacterial artificial chromosome)



www.genome.gov

150.10^6 bp = 150 Mb = size of a typical chromosome

3000 Mb = 3 Gb = human genome

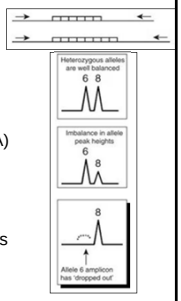
Centrum voor Medische Genetica

12 titel 18-5-2014

Whole genome amplification

from 6 pg (single cell) to several µg of DNA (5.10^6 x)

amplification problems =>
complicate array data analysis

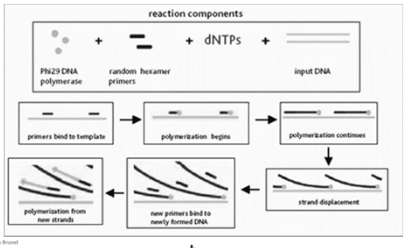


bias
allele drop-out (ADO) and preferential amplification (PA)
amplification errors
incomplete genome coverage

different protocols => different downstream applications

Whole genome amplification: MDA

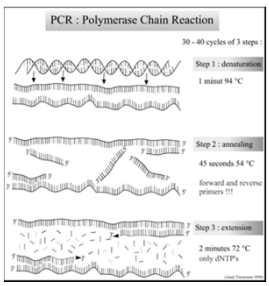
- Molecular Displacement Amplification, (MDA)
  isothermal amplification (30°C) => DNA fragments up to 70 kb,
  low error rates



Dean et al., 2002

MDA vs PCR

thermocycling

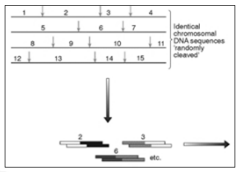


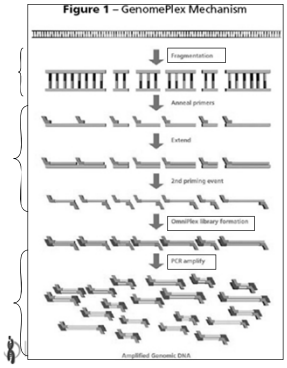
http://users.ugent.be/~avierstr/principles/pcr.html

Whole genome amplification: library based

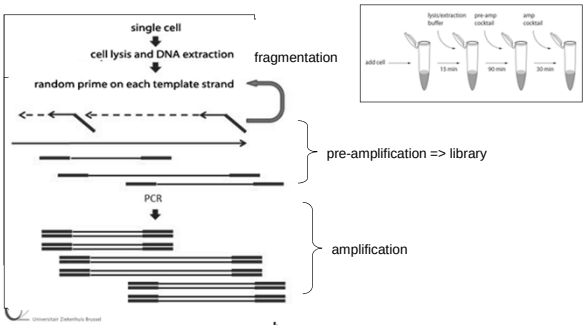
GenomePlexTM WGA (Sigma)
or PicoPlexTM WGA (Rubicon)

- fragmentation
- library preparation
- universal-primer PCR





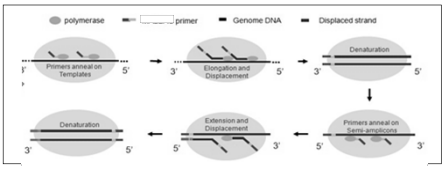
Whole genome amplification: library based



Centrum voor Medische Genetica

Whole genome amplification: library based

pre-amplification => library

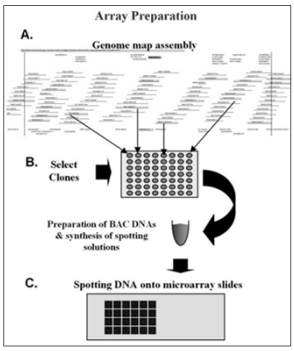


1 cycle	95°C	2 min
12 cycles	95°C	15 sec
	15°C	50 sec
	25°C	40 sec
	35°C	30 sec
	65°C	40 sec
	75°C	40 sec
1 cycle	4 °C	hold

Centrum voor Medische Genetica

BAC array preparation for array CGH

Resolution = clone size distance and clone #



www.molecular-cancer.com

Various platforms

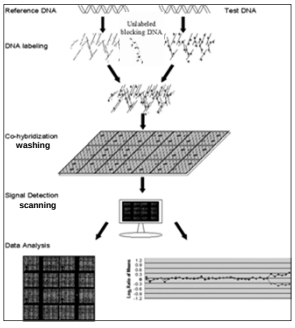
BAC arrays	Oligo arrays	SNP+whole genome
80-200 kb	Oligos are shorter 25-mer to 80-mer	Similar to Oligo array, but incorporate Bi-allelic probes

genome-wide arrays with 3000 BAC clones every 1 Mb resolution is 10 Mb

genome-wide array with 1.8 10^6 clones resolution = 10-20 kb

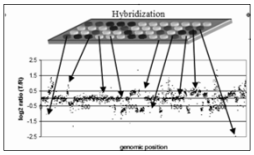
Centrum voor Medische Genetica

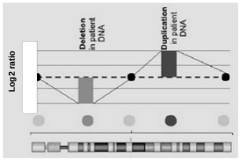
Array CGH: workflow



Centrum voor Medische Genetica

Array CGH: interpretation



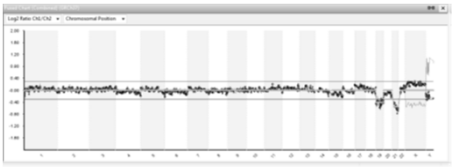


	# copies test	# copies reference	log2 (test/reference)
deletion	1	2	-1
normal	2	2	0
duplication	3	2	0.58

Abdullah Alqallaf and Ali Hajjiah, 2011

Centrum voor Medische Genetica

Array CGH

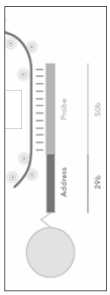


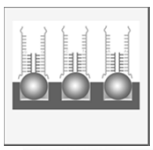
detection of aneuploidy of whole chromosomes or chromosome segments

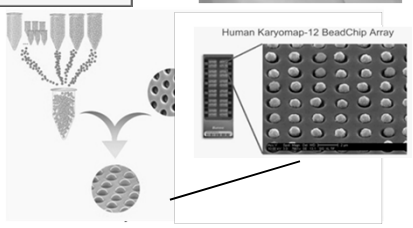
http://www.cambridgebluegnome.com

Centrum voor Medische Genetica

SNP bead array preparation

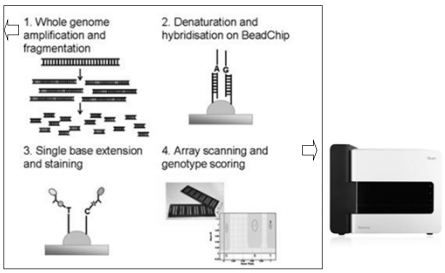






SNP bead array: workflow

MDA based



Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Medische Genetica

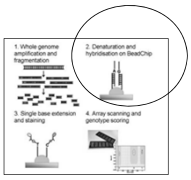
SNP array: principle

target

denaturation and hybridisation on beadChip

probe

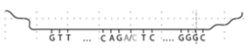
LaFramboise T , 2009



Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

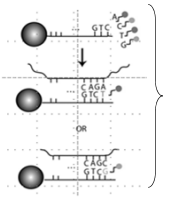
Centrum voor Medische Genetica

SNP array: principle



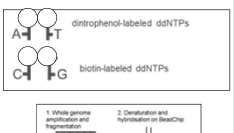
target

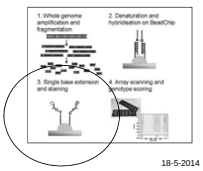
denaturation and hybridisation on beadChip



probe

single base extension





LaFramboise T , 2009

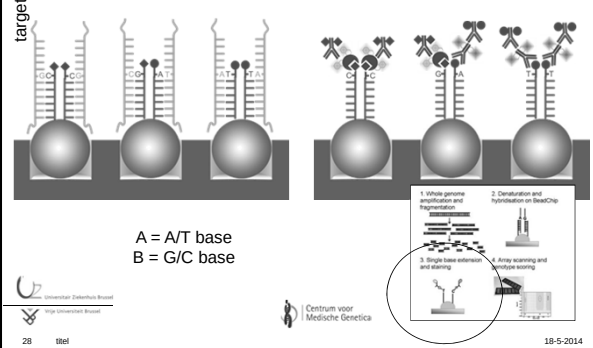
Universitair Ziekenhuis Brussel
Vrije Universiteit Brussel

Centrum voor Medische Genetica

SNP array: principle

target removal and staining

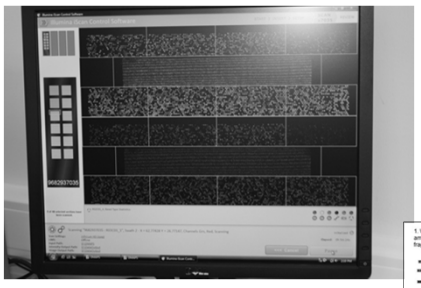
target



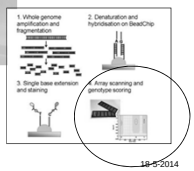
A = A/T base
B = G/C base

Centrum voor Medische Genetica

SNP bead array

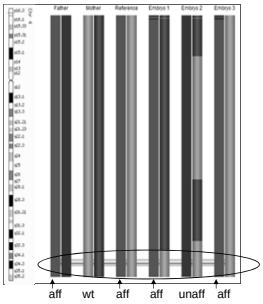


A = A/T base
B = G/C base
NC = no call



Centrum voor Medische Genetica

SNP array: interpretation



genotype information

1) identify informative SNPs in region of interest

2) phase SNPs in embryo vs reference

Centrum voor Medische Genetica

SNP array: interpretation

father	mother	reference	embryo	phase
A**B**	AA	A**B**	A**B**	in phase
AB	BB	BB	**A**B	out of phase
AA	BB	not informative		
A**B**	AA	AA	AA	in phase
A**B**	AA	A**B**	AA	out of phase
AB	BB	**A**B	BB	out of phase
AB	AB	not informative		

genotype information

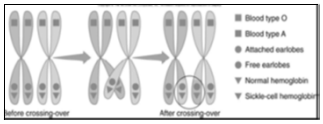
1) identify informative SNPs in region of interest

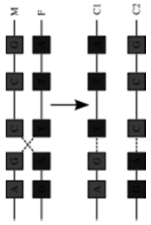
2) phase SNPs in embryo vs reference

examples:
informative SNP in blue

SNP array: interpretation

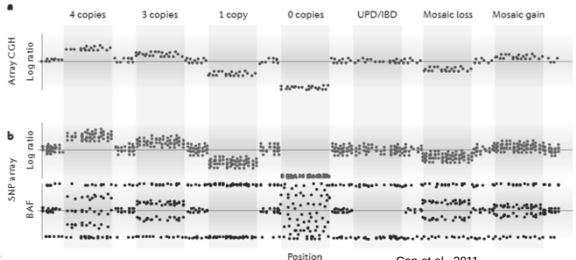
- Genotyping relies on informative SNPs blocks
  Sister chromatid exchange during prophase of meisosis => recombination => haploblocks





SNP array: interpretation

genotype + copy number information



Can et al., 2011

SNP array: interpretation

CNV type	Possible SNP genotypes	Expected A+B signal	Expected BAF
Homozygous gain	*AAAA*	4	0
	AAAB	4	0.25
	AABB	4	0.5
	ABBB	4	0.75
	BBBB	4	1
Hemizygous gain	*AAA*	3	0
	AAB	3	0.33
	ABB	3	0.67
	BBB	3	1
Normal	*AA*	2	0
	AB	2	0.5
	BB	2	1
Hemizygous loss	*A_*	1	0
	*B_*	1	1
Homozygous loss	*_ _*	0	Undefined

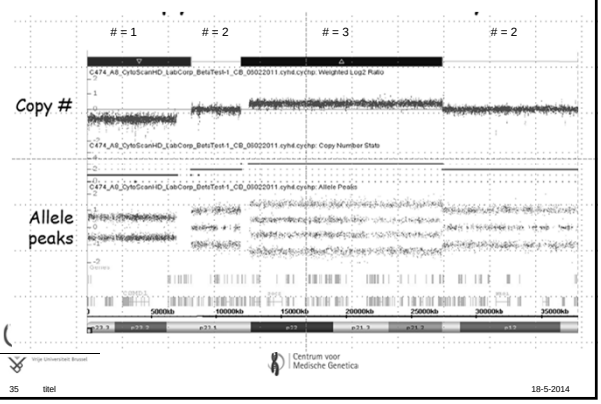
#B in AA= 0/2 = 0

#B in AB= 1/2 = 0.5

#B in BB= 2/2 = 1

Centrum voor Medische Genetica

SNP array: interpretation



Centrum voor Medische Genetica

Summary

- PGD/PGS: standard single cell assays > still labour intensive and time consuming
- Replaced by new technologies > genome-wide
  - universal single-cell WGA + array platforms
- Array CGH for chromosomal aberrations and PGS (no monogenic disorders)
- SNP array for monogenic disorders, chromosomal aberrations and PGS under development
- new ethical challenges: incidental findings

Centrum voor Medische Genetica

References

- SenGupta SB, Delhanty JD. (2012)
Preimplantation genetic diagnosis: recent triumphs and remaining challenges
Expert Rev Mol Diagn.12(6):585-92. Review.

- Checa MA, Alonso-Coello P, Solà I, Robles A, Carreras R, Balasch J. (2009)
IVF/ICSI with or without preimplantation genetic screening for aneuploidy in couples without genetic disorders: A systematic review and meta-analysis.
J Assist Reprod Genet. 26(5):273-83. Review.

-Dean FB, Hosono S, Fang L, Wu X, Faruqi AF, Bray-Ward P, Sun Z, Zong Q, Du Y, Du J, Driscoll M, Song W,Kingsmore SF, Egholm M, Lasken RS. (2002)
Comprehensive human genome amplification using multiple displacement amplification.
Proc Natl Acad Sci U S A. 99(8):5261-6.

- Spits C, Le Caignec C, De Rycke M, Van Haute L, Van Steirteghem A, Liebaers I, Sermon K. (2006)
Whole-genome multiple displacement amplification from single cells.
Nat Protoc.1(4):1965-70.

References

- Steemers FJ, Chang W, Lee G, Barker DL, Shen R, Gunderson KL (2006)
Whole-genome genotyping with the single-base extension assay.
Nat Methods 3:31-33

- LaFramboise T. (2009)
Single nucleotide polymorphism arrays: a decade of biological, computational and technological advances.
Nucleic Acids Res. 37(13):4181-93.

- Munné S. (2012)
Preimplantation genetic diagnosis for aneuploidy and translocations using array comparative genomic Hybridization.
Curr Genomics.13(6):463-70.

- Gunderson KL, Steemers FJ, Lee G, Mendoza LG, Chee MS (2005)
A genome-wide scalable SNP genotyping assay using microarray technology.
Nat genet 37:549-554

Is trophectoderm biopsy and subsequent PGD the new tool for embryo selection for a subgroup of patients?

Mandy Katz-Jaffe, Ph.D.

Scientific Director
Colorado Center for Reproductive Medicine

Conflict of Interest Disclosure

Mandy Katz-Jaffe Ph.D.

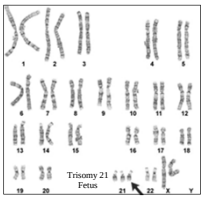
Has no real or apparent
conflicts of interest to report.

Learning Objectives

Participants will gain an understanding of:

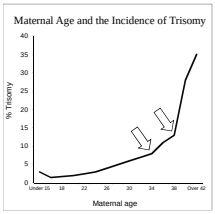
1) Trophectoderm biopsy
2) Clinical applications of aneuploidy screening
3) Associated outcomes for subgroups of infertility patients

Chromosome Aneuploidy



Aneuploidy is the most common chromosome abnormality in human conceptions, and is the leading cause of miscarriage and congenital birth defects

Chromosome Aneuploidy



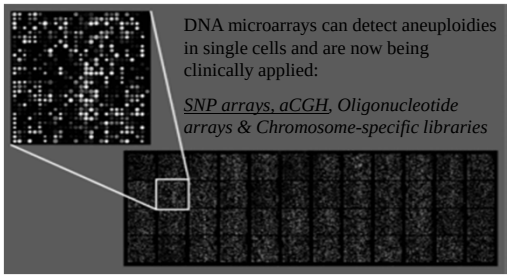
Maternal age is the highest risk factor for the incidence of fetal trisomies

Maternal age is also the major contributor to human infertility

Primarily due to:

- Progressive oocyte depletion
- Increase in maternal meiotic errors resulting in chromosome aneuploidy

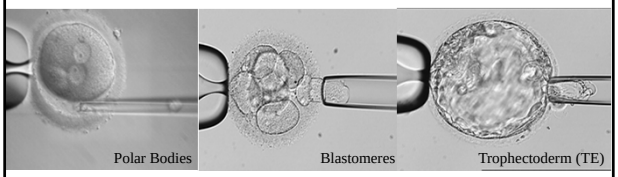
Aim: To select euploid embryos (correct number of chromosomes) for transfer in ART



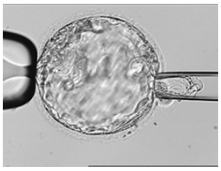
DNA microarrays can detect aneuploidies in single cells and are now being clinically applied:

SNP arrays, aCGH, Oligonucleotide arrays & Chromosome-specific libraries

Sources of Genetic Material



Blastocyst TE Biopsy

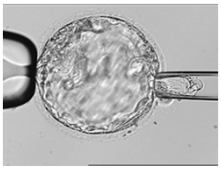


Advantages include:

- Competent *in vitro* embryo

A meta-analysis reviewed 23 RCTs and concluded that blastocyst transfer resulted in a significant increase in live birth rates (Glujovsky et al, 2012).

Blastocyst TE Biopsy

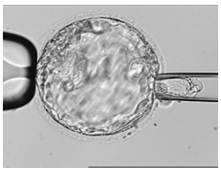


Advantages include:

- Competent *in vitro* embryo
- Reduced chromosomal mosaicism

Mitotic errors are observed during human preimplantation development resulting in chromosomal mosaicism (defined as the presence of more than one chromosome complement). Several studies have observed a lower rate of mosaicism in blastocysts compared to cleavage stage embryos (Reviewed by Mantikou et al, 2012).

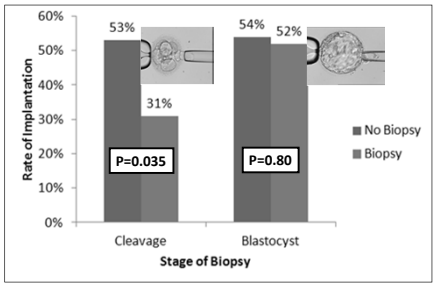
Blastocyst TE Biopsy



Advantages include:

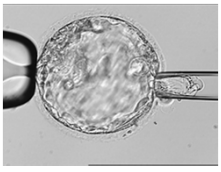
- Competent *in vitro* embryo
- Reduced chromosomal mosaicism
- Several cells for testing
- Minimal impact of TE biopsy

Impact of Embryo Biopsy



Scott et al., 2013

Blastocyst TE Biopsy



Advantages include:

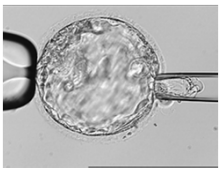
- Competent *in vitro* embryo
- Reduced chromosomal mosaicism
- Several cells for testing
- Minimal impact of biopsy

Potential disadvantages:

- Only testing TE cells

Isolation and re-analysis of ICM and TE cells from aneuploid blastocysts have revealed no preferential allocation of abnormal cells between the two cell lineages (Capalbo et al, 2013)

Blastocyst TE Biopsy



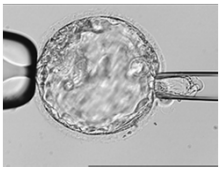
Advantages include:

- Competent *in vitro* embryo
- Reduced chromosomal mosaicism
- Several cells for testing
- Minimal impact of biopsy

Potential disadvantages:

- Only testing TE cells
- Cryopreservation

Blastocyst TE Biopsy



Cryopreservation is an essential component of blastocyst biopsy when a D5 transfer is preferred.

Only limited time (<4hrs) would be available for CCS analysis between the TE biopsy and a D5 fresh transfer.

Roy et al, 2014 reported a 94.4% survival rate of vitrified-warmed blastocysts and excellent neonatal outcomes following SET (n=645).

FET Results in Healthier Babies and Better Overall Outcomes

Roque et al, 2013

- Meta-analysis revealed significantly higher clinical pregnancy rates following FET versus fresh transfer

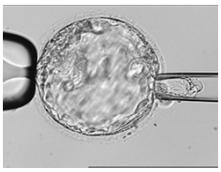
Wennerholm et al, 2013

- Population based cohort study revealed FET singletons have a better perinatal outcome compared with singletons born after fresh IVF and ICSI

Ishihara et al, 2014

- Improved general perinatal outcome of pregnancy but increased risk of maternal complications including placenta accreta and pregnancy-induced hypertension

Blastocyst TE Biopsy



Advantages include:

- Competent *in vitro* embryo
- Reduced chromosomal mosaicism
- Several cells for testing
- Minimal impact of biopsy

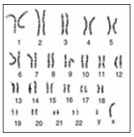
~~Potential disadvantages:~~

- ~~Only testing TE cells~~
- ~~Cryopreservation~~

CCRM IRB Approved Clinical Study (2007-Current)

Trophectoderm Biopsy

Blastocyst Vitrification

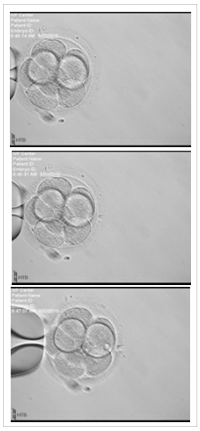


mCGH (Reprogenetics)
SNP Microarray & qPCR (RMA-NJ)

Frozen Embryo Transfer (FET)

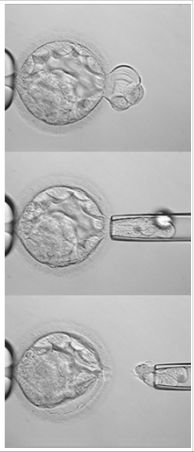
Based on CCS result only

Schoolcraft et al, 2009 & 2011; Schoolcraft & Katz-Jaffe, 2013



Day 3 Cleavage Stage Embryo

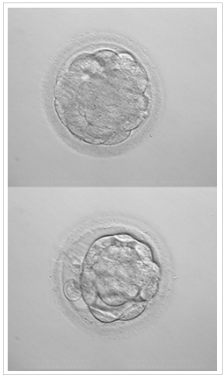
Channel Opening for TE Biopsy



Hatching Blastocyst

Trophectoderm Biopsy

Post Trophectoderm Biopsy

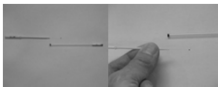


10 minutes Post TE-Biopsy

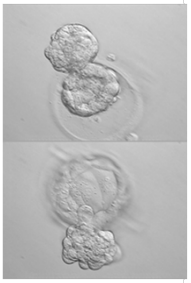
1 hour Post TE-Biopsy

Equilibration
7.5% EG,
7.5% DMSO

Dehydration
15%EG, 15% DMSO
.5M Sucrose



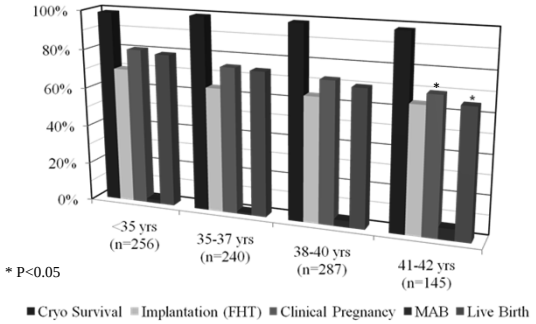
Cryotop - Kuwuyama et al, 2008



Post Warming

Prior to Transfer

BC-CCS Cycle Outcome 2007-2013



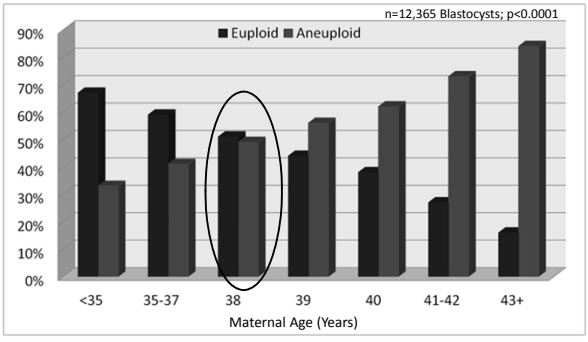
Schoolcraft et al, 2009 & 2011; Schoolcraft & Katz-Jaffe, 2013

Single Frozen Blastocyst Transfer with and without CCS

	SBT CCS (n=347 FETs)	SBT non-CCS (n=272 FETs)	
Maternal Age	37.9 years	36.8 years	p=0.0006
	±3.7	±4.8	
Implantation Rate (FHT)	65.1%	52.6%	p=0.0017
Biochemical Pregnancy	79.8%	65.8%	p=0.0001
Clinical Pregnancy (FHT)	62.8%	51.1%	p=0.0041
Ongoing Pregnancy and Live Birth Rate	60.0%	43.8%	p<0.0001
MAB	4.6%	14.4%	p=0.0016

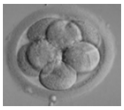
Schoolcraft & Katz-Jaffe, 2013

Aneuploidy has a Significant Association with Maternal Age

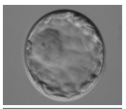


Schoolcraft et al, 2009 & 2011; Schoolcraft & Katz-Jaffe, 2013

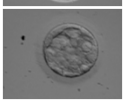
Embryo Morphology & Euploidy



No correlation between D3 morphology, time lapse and blastocyst chromosome constitution



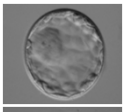
Euploidy with good quality D5 blastocysts



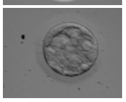
Aneuploidy with poor quality blastocysts

Schoolcraft et al, 2009 & 2011; Schoolcraft & Katz-Jaffe, 2013

D5 Morphology is NOT Absolute



= Aneuploid



= Euploid

Schoolcraft et al, 2009 & 2011; Schoolcraft & Katz-Jaffe, 2013

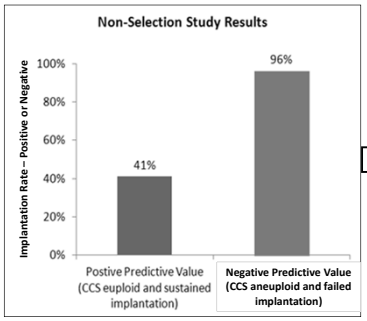
Single Blastocyst Fresh D6 Transfer – Randomized Pilot Study

Study Eligibility:
- <35 years maternal age
- Regular ovulation
- No previous IVF
- Infertility etiology was tubal factor or male factor or both
- D3 FSH <10IU/l
- D3 Estradiol <60pg/ml
- Normal intrauterine contour

	aCGH (n=55)	Morphology alone (n=48)	P value
Grade 5/6	31	28	
Grade 4	21	19	0.677
Grade 3	3	1	
Clinical Pregnancy	70.9%	45.8%	0.017
Ongoing Pregnancy	69.1%	41.7%	0.009
MAB	2.6%	9.1%	0.597

Yang et al., 2013

Negative and Positive Prediction for Reproductive Potential



P<0.001

Scott et al., 2012

RCT – CCS versus Nonintervention

- n=155 patients; 21-42 years and 0-1 previous failed IVF cycle
- Study Group = Euploid blastocyst transfer on D6 after D5 biopsy
- Control Group = Day 5 blastocyst transfer based on morphology

	Study (CCS)	Control (Morphology)
# Patients	72	83
Age	32.2	32.4
Clinical Implantation	79.8 %	63.2 %*
Sustained Implantation	66.4 %	47.9 %*
Delivery per Cycle	84.7%	67.5 %*

*P<0.05; Forman et al., 2013

RCT – CCS versus Morphology Selection

- <42 maternal years and 0-1 previous failed IVF cycle
- Study Group = single euploid blastocyst transfer
- Control Group = double blastocyst transfer based on morphology

	Study (SET)	Control (DET)
# Patients	89	86
Age	34.5	35.1
Clinical PR	69 %	81 %
Ongoing PR	61 %	65 %
Multiples	0	48 %*

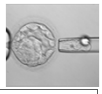
*P<0.05; Forman et al., 2013

Infertile patients of maternal age >35 years were computer randomized at oocyte retrieval into either:

Control Group

Test Group

All embryos are grown to the blastocyst stage



Day 5 Fresh Transfer
Embryo selection based on morphology

Surplus blastocysts biopsied for CCS prior to vitrification

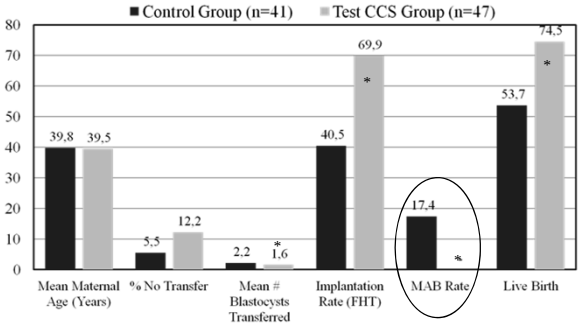
Blastocyst biopsy for CCS

CCS using SNP microarray technology

Frozen Embryo Transfer
Euploid embryos only

Schoolcraft & Katz-Jaffe, 2013

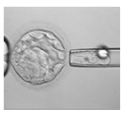
IVF Cycle and Transfer Outcome

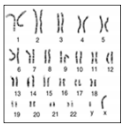


Schoolcraft & Katz-Jaffe, 2013 Significance = P<0.05

Unexplained RIF Group (n=130)
≥3 consecutive IVF failures

Unexplained Repeated Miscarriage (RM) (n=77)
≥3 consecutive pregnancy losses





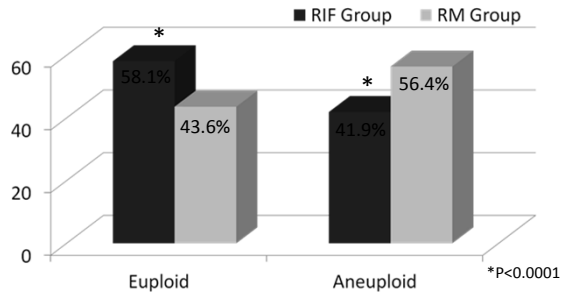
All embryos are grown to the blastocyst stage for trophectoderm biopsy

CCS using qPCR (RMA-NJ)

Frozen Embryo Transfer
Euploid embryos only

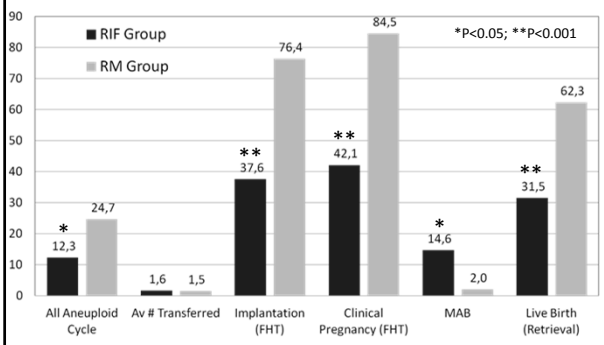
RIF and RM patients had no other infertility indications & no significant differences in cycle parameters

Patients in the RM group are 1.35 times more likely to have an aneuploid blastocyst



No significant difference in blastocyst development, blastocyst quality or embryo gender

IVF BC-CCS Cycle Outcome



Katz-Jaffe et al, 2013

Conclusion:

- Trophectoderm biopsy with CCS increases the likelihood that an individual blastocyst will result in a chromosomally normal live birth, specifically for infertile AMA women.
- RIF patients did experience some benefit from the transfer of a euploid blastocyst but not as significant as was observed for RM patients of equivalent maternal age.
- Even though embryo euploidy is essential for healthy fetal development, other factors including flaws in endometrial receptivity, embryonic function, and embryo-endometrium dialogue should be further investigated in unexplained RIF.

Colorado Center for Reproductive Medicine

William B Schoolcraft, MD
Eric Surrey, MD
Debra Minjarez, MD
Rob Gustofson, MD
John Stevens & IVF Lab
Megan Schweitz

RMA-NJ

Richard T Scott Jr, MD
Nathan Treff, PhD

References

- Capalbo et al, 2013. FISH reanalysis of ICM and TE samples of previously arra-CGH screened blastocysts shows high accuracy of diagnosis and no major diagnostic impact of mosaicism at the blastocyst stage. *Hum Reprod*
- Forman et al, 2013. In vitro fertilization with single euploid blastocyst transfer: a randomized controlled trial. *Fertil Steril*
- Glujovsky et al, 2012. Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology. *Cochrane Database Syst Rev*
- Ishihara et al, 2014. Impact of frozen-thawed single-blastocyst transfer on maternal and neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. *Fertil Steril*
- Katz-Jaffe et al, 2013. Can the transfer of euploid blastocysts in a frozen embryo transfer overcome repeated IVF failure? *Fertil Steril*
- Mantikou et al, 2012. Molecular origin of mitotic aneuploidies in preimplantation embryos. *Biochim Biophys Acta*
- Roque et al, 2013. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. *Fertil Steril*
- Roy et al, 2014. Single-embryo transfer of vitrified-warmed blastocysts yields equivalent live-birth rates and improved neonatal outcomes compared with fresh transfers. *Fertil Steril*
- Schoolcraft WB and Katz-Jaffe MG. (2013) Comprehensive chromosome screening of trophectoderm with vitrification facilitates elective single-embryo transfer for infertile women with advanced maternal age. *Fertil Steril*
- Schoolcraft et al, 2009. Clinical application of comprehensive chromosomal screening at the blastocyst stage. *Fertil Steril*
- Schoolcraft e al, 2011. Live birth outcome with trophectoderm biopsy, blastocyst vitrification and single nucleotide polymorphism microarray based comprehensive chromosome screening in infertile patients. *Fertil Steril*
- Scott et al., 2013. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. *Fertil Steril*
- Wennerholm et al, 2013. Perinatal outcomes of children born after frozen-thawed embryo transfer: a Nordic cohort study from the CoNARTaS group. *Hum Reprod*
- Yang et al, 2013. Selection of euploid blastocysts for cryopreservation with array comparative genomic hybridzation (aCGH) results in increased implantation rates in subsequent frozen and thawed embryo transfer cycles. *Mol Cytogenet*

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Dealing with miscarrige

- Anne Louise Lunøe
- RN. Study Nurse, Danish Recurrent Miscarrige Unit, Fertility clinic Rigshospitalet, Copenhagen, Denmark.

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Conflict of interest

- I hereby confirm that I do not have any commercial and financial relationships related to this presentation and its contents

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

REGION

Outlines

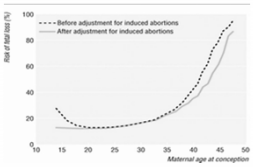
- Definitions Miscarriage/Recurrent miscarriage
- The Danish Recurrent Miscarriage Unit – Organisation – Investigations – Treatment – Care
- The Danish Recurrent Miscarriage Unit – Cases
- The value of The Recurrent Miscarriage Unit

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Miscarriage

- Pregnancy loss before the 22th week of pregnancy
- Approximately 25% of pregnancies result in a miscarriage
- 10% of these are pregnancies confirmed by ultrasound



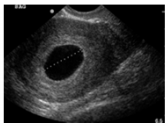
Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Concepts

- Biochemical pregnancy

- Miscarriage



Rigshospitalet, University of Copenhagen

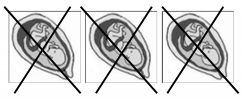
Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Recurrent Miscarriage (RM)

1-3% of women

50% unexplained

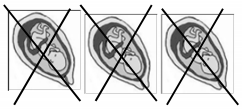


Primary (60%)

PRM

♂

♀



Secondary (40%)

SRM

Rigshospitalet, University of Copenhagen

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Recurrent miscarriage unit, Rigshospitalet Copenhagen

- Located at The Fertility Clinic, Rigshospitalet
- 3 MD's, 2 RN, 1 Ph.d student, 1 secretary, research students
- 200 referred women per year
- Referrals from the whole country

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Investigations at The Recurrent Miscarrige Unit

- Pregnancy history, diseases, family diseases,

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Investigations at The Recurrent Miscarrige Unit

- Pregnancy history, diseases, family diseases
- **Lifestyle**

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Investigations at The Recurrent Miscarrige Unit

- Pregnancy history, diseases, family history
- Lifestyle
- Thrombophilia screening,Thyroid screening, autoantibodies, tissue typing, karyotyping, endocrine screening
- Assessment of the uterine cavity

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Comments before diagnosis

- ***"But you get pregnant so easily"***
- ***"Next time will be the lucky time"***
- ***"There was probably something wrong with the foetus"***
- ***"Maybe you shouldn't have any more children"***
- ***"Learn to be happy with the child you already have"***

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

- TLC – Tender Loving Care

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Tender Loving Care

- Everyone gets TLC

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

TLC

Call at the time of a pos. test
35 45 84 86
(blood tests)

2 days later:
5th gestational week
(blood tests)

App.1 week later:
6th gestational week
(blood tests)

App. 1 week later:
7th gestational week
(first scan)

App. 1 week later:
8th gestational week
(second scan)

App. 1½ weeks later:
10th gestational week
(third scan)

App. 2 weeks later:
12th gestational week
(fourth scan)

Nuchal translucency scan:
between 12th og 14th gestational week (11+3 to13+6)
Book an appointment yourself.

App. 2 weeks later:
16th gestational week
(last week)

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

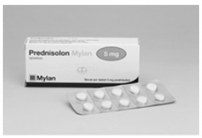
- TLC – Tender Loving Care
- **IVIG**

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

- TLC – Tender Loving Care
- IVIG
- **Prednisolon**



Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

- TLC – Tender Loving Care
- IVIG
- Prednisolon
- **Levothyroxin**

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

- TLC – Tender Loving Care
- IVIG Prednisolon
- Levothyroxin
- **Low molecular heparin**

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

- TLC – Tender Loving Care
- IVIG
- Prednisolon Levothyroxin
- Low molecular heparin
- **Progesteron**

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Treatment

- TLC – Tender Loving Care
- IVIG
- Prednisolon
- Levothyroxin
- Low molecular heparin
- Progesteron
- **Folic acid**

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

TLC

The value of psychological support in improving pregnancy outcome has not been tested in the form of a randomised controlled trial. However, data from several non-randomised studies have suggested that attendance at a dedicated early pregnancy clinic has a beneficial effect, although the mechanism is unclear."
(RCOG Guideline # 17: 2011, p. 13)

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Care

- Quarterly information meetings

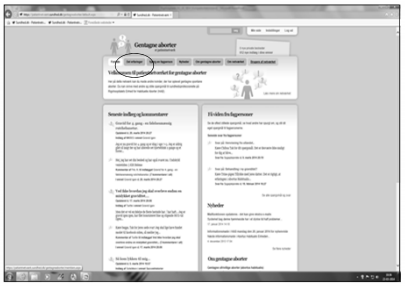
- Daily telephone consultations

- Online patient network

Rigshospitalet

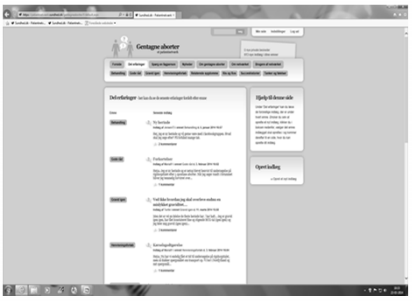
FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Online Patient network
”Reccurrent miscarrige” ”rød ring”



Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN



Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Case SRM

- 30 years
- 2010-boy
- 2012-2013: 3 pregnancy losses between week 6-10
- 2013 referred to Recurrent Miscarrige Unit
- Normal investigations
- TLC
- Status

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

”Pregnant for the 4th time – a roller coaster ride”

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Case PRM

- 38 years old
- 4 losses week 5-8
- Hypothyroidism since the age of 19
- IVIG week 4 -13
- TLC week 13-16
- Birth of a live girl

Rigshospitalet

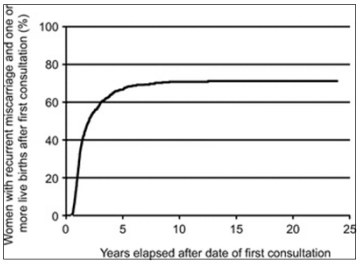
FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

”The Epidemic goes on”

Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Women with at least one child after referral, investigations and treatment



Rigshospitalet

FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

The strenghts of The Recurrent Miscarrige Clinic Rigshospitalet, Copenhagen

- Small unit
- Few staff members
- All around ”TLC”

Supporting women during waiting periods

H. Ockhuijsen, A. van den Hoogen, M. Eijkemans, N. Macklon, J. Boivin
H.D.L. Ockhuijsen (RN, MSc)

University Medical Center Utrecht

Disclosure

Hetty Ockhuijsen has no relevant conflict of interest with any commercial interest and has nothing to disclose

UMC Utrecht

Learning objectives

At the end of this presentation participant's should be able to

- Describe the impact of distress in patients during waiting periods
- Describe a coping process
- Describe the PRCI intervention for waiting periods
- Describe the results of a quantitative and qualitative study

UMC Utrecht

Presentation contents

- Introduction
- Quantitative research
- Qualitative research
- Conclusion

UMC Utrecht

Quantitative and qualitative research

- Difference between quantitative and qualitative research

UMC Utrecht

Medical waiting periods

Waiting for health care is identified as an unspecified yet measurable period of time between identification of a healthcare problem and its diagnosis and treatment, when clients experience **uncertainty** and **powerlessness** whilst **anticipating** a (disease) **outcome** (Fogarty & Cronin, 2008)

- Outcome unpredictable
- Outcome cannot be changed or controlled
- High levels of anxiety and uncertainty
- Difficult to cope with

UMC Utrecht

Coping with waiting periods

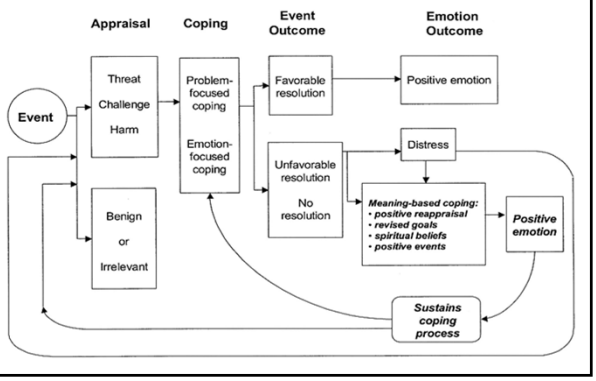
Definition coping

Lazarus and Folkman (1984) define coping as constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person.

- Problem focussed coping
- Emotion focussed coping

UMC Utrecht

Revised model of stress & coping (Folkman, 1997,2008)



Positive Reappraisal Coping Intervention

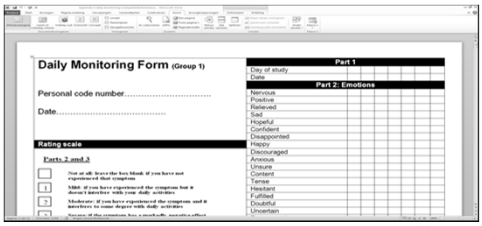
- Medical waiting periods
  Boivin & Lancastle, 2010, Women's Health
- Stress and coping theory
  Lazarus & Folkman, 1984
- MRC-Framework
  Craig et al. 2008, BMJ

UMC Utrecht

Lancastle & Boivin, 2011, Hum Reprod

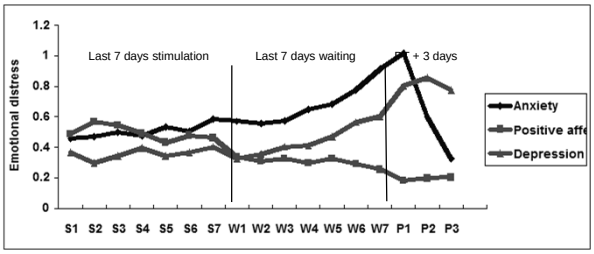
Daily Record Keeping (DRK)

- Developed in the UK (Boivin, 1997)
- Daily measures about emotions, physical symptoms, coping-strategies



UMC Utrecht

Daily Record Keeping (DRK)



UMC Utrecht

Boivin & Lancastle, 2010, Women's Health

PRCI and IVF waiting period

The aim of this study was to investigate the effect of the PRCI on psychological well-being of women waiting for the results of an IVF/ICSI treatment

- Primary outcome:
  - general anxiety
- Secondary outcomes:
  - depression
  - positive and negative affect
  - intervention evaluation
  - treatment outcome

UMC Utrecht

Methods/Design

Three armed randomized controlled trial

- PRCI intervention : PRCI & Daily monitoring
- Monitoring control: Daily monitoring
- Routine care

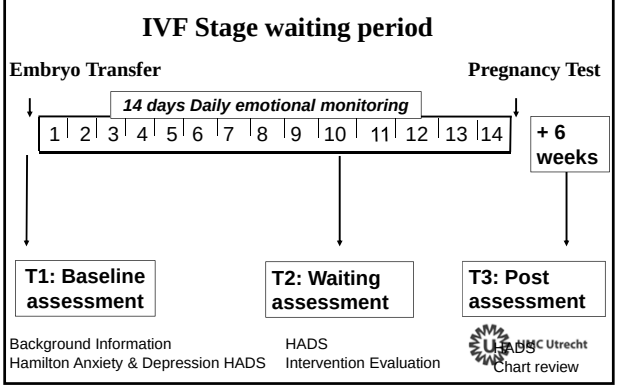
UMC Utrecht

Methods/Participants

- Recruitment over 20 months
- Opt in method
- Inclusion criteria
  - Women undergoing a stimulated or cryopreserved IVF/ICSI treatment
- Exclusion criteria
  - Insufficient knowledge of the Dutch language
- Power calculation
  - 95% power to detect a medium effect size with α=0.05 & including 20% attrition → 124 per RCT group

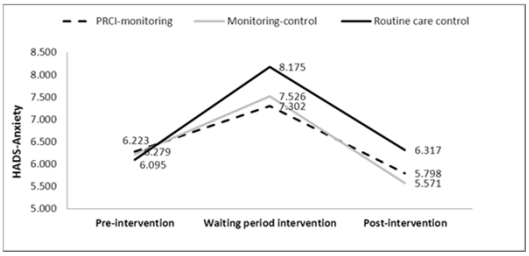
UMC Utrecht

Data collection schedule



UMC Utrecht

Results RCT anxiety

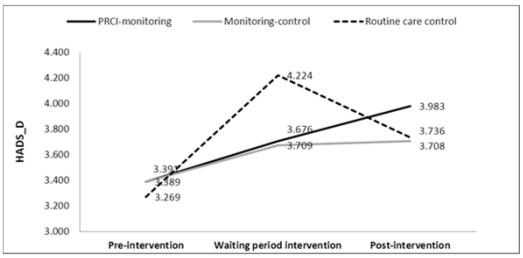


Anxiety	p
ME Group	0.125
ME Time	0.000
Group*Time	0.129

Results based on multilevel modelling controlling for baseline variable counselling before treatment.

UMC Utrecht

Results RCT depression



Depression	p
ME Group	0.728
ME Time	0.001
Group*Time	0.241

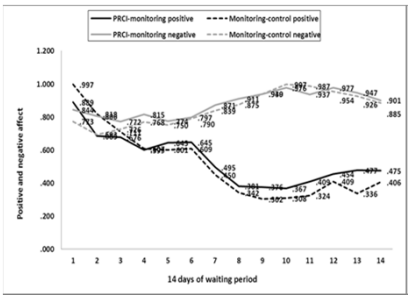
Results based on multilevel modelling controlling for baseline covariates:
Use of counselling before treatment.

UMC Utrecht

Results Daily monitoring groups Positive and negative affect

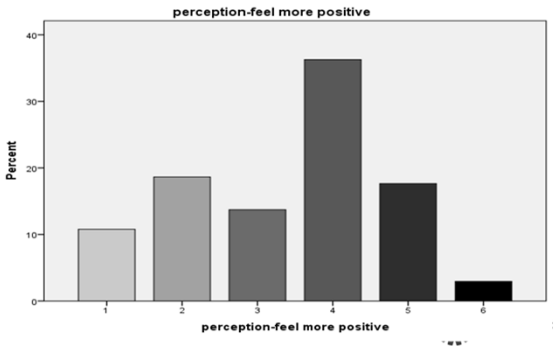
Variable	
Positive affect	p-value
Group	0.231
Time	0.000
Group*Time	0.000

Negative affect	p-value
Group	0.281
Time	0.000
Group*Time	0.066

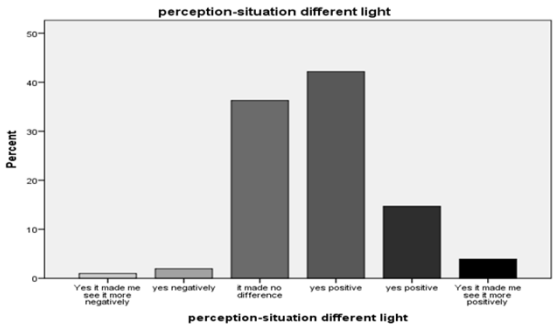


UMC Utrecht

Results intervention evaluation



Results intervention evaluation



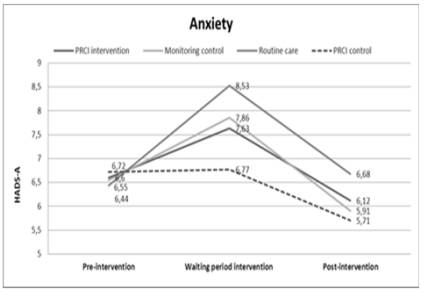
Results treatment outcome

Chi-Square Tests	PRCI monitoring	Monitoring control	Routine care	P-value
Clinical pregnancy	24.4%	26.5%	23.0%	0.83
Clinical pregnancy with heartbeat	24.4%	22.2%	20.4%	0.76

UMC Utrecht

Results 4 groups primary outcome anxiety

Variable	p
Anxiety	
Group	0.017
Time	0.000
Group*Time	0.004



UMC Utrecht

Results 4 groups treatment outcome

Chi-Square Tests	PRCI monitoring	Monitoring control	Routine care	PRCI control	P-value
Clinical pregnancy	24.4%	26.5%	23.0%	39.8%	0.03
Clinical pregnancy with heartbeat	24.4%	22.2%	20.2%	34.4%	0.10

UMC Utrecht

Background PRCI and miscarriage(s)

- Miscarriage (s) stressfull experience
- Anxiety and depression in subsequent pregnancy
- PRCI suitable for pregnant women with a miscarriage history?

UMC Utrecht

Three waiting periods

- Miscarriage waiting period
- Conception waiting period
- Pregnancy waiting period

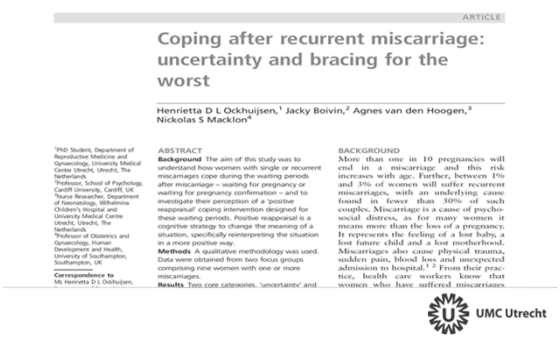
UMC Utrecht

Qualitative research

- Focus groups
- Interviews pregnant women with a history of miscarriage(s)
- Mixed method Interviews and questionnaire

UMC Utrecht

Focus groups



ARTICLE

Coping after recurrent miscarriage: uncertainty and bracing for the worst

Henrietta D L Ockhuijsen,[1] Jacky Boivin,[2] Agnes van den Hoogen,[3] Nickolas S Macklon[4]

[1]PhD Student, Department of Reproductive Medicine and Gynaecology, University Medical Centre Utrecht, Utrecht, The Netherlands [2]Professor, School of Psychology, Cardiff University, Cardiff, UK [3]Nurse Researcher, Department of Neonatology, Wilhelmina Children's Hospital and University Medical Centre Utrecht, Utrecht, The Netherlands [4]Professor of Obstetrics and Gynaecology, Human Development and Health, University of Southampton, Southampton, UK

Correspondence to
Ms Henrietta D L Ockhuijsen,

ABSTRACT

Background The aim of this study was to understand how women with single or recurrent miscarriages cope during the waiting periods after miscarriage – waiting for pregnancy or waiting for pregnancy confirmation – and to investigate their perception of a 'positive reappraisal' coping intervention designed for these waiting periods. Positive reappraisal is a cognitive strategy to change the meaning of a situation, specifically reinterpreting the situation in a more positive way.

Methods A qualitative methodology was used. Data were obtained from two focus groups comprising nine women with one or more miscarriages.

Results Two core categories, 'uncertainty' and

BACKGROUND

More than one in 10 pregnancies will end in a miscarriage and this risk increases with age. Further, between 1% and 3% of women will suffer recurrent miscarriages, with an underlying cause found in fewer than 50% of such couples. Miscarriage is a cause of psycho-social distress, as for many women it means more than the loss of a pregnancy. It represents the feeling of a lost baby, a lost future child and a lost motherhood. Miscarriages also cause physical trauma, sudden pain, blood loss and unexpected admission to hospital.[1,2] From their practice, health care workers know that women who have suffered miscarriages

UMC Utrecht

PRCI and Miscarriage Qualitative research

Research questions

- How do women experience and cope during the miscarriage, conception, and early pregnancy waiting period?
- How do pregnant women with a history of miscarriage(s) experience the use of a Positive Reappraisal Coping Intervention (PRCI) and Daily Record Keeping (DRK) chart?

UMC Utrecht

Setting and sampling

Women attending an Early Pregnancy Unit and/or Recurrent Miscarriage Clinic in a University Medical Centre in the Netherlands.

- Pregnant or the wish to become pregnant again
- 1, 2, 3 or more miscarriages
- Older or younger than 35 years of age
- Speaking the Dutch language

UMC Utrecht

Methods

- Semi structured face to face interviews (n=24)
- Women used the PRCI and DRK during first 3 weeks of pregnancy (n=13)
- Data analysis
  - Thematic analysis
    - First phase: descriptive stage
    - Second phase: interpretive stage
    - Third phase: overarching themes

UMC Utrecht

Results interviews emotions and coping with waiting periods

Three themes

- Facing loss during miscarriage period
- Dealing with waiting during conception period
- Searching for control during pregnancy period

Overaching theme

- Balancing between loss of control and searching for control

UMC Utrecht

Facing loss

Emotions

"The first was also an early miscarriage, that was just disappointment, you do not know very much, you're still a little inexperienced but it is becoming heavier every next time". [29-5]

Coping

"Well…yes…talked a lot about it with my boyfriend and friends. On the one hand it was fine on the other hand not. None of my friends have experienced this so it is quite difficult for them to understand. And then sometimes they said…..well at least you know that you can become pregnant….I got that kind of remarks".[27-3]

UMC Utrecht

Dealing with waiting

Emotions

"The last time I was actually very impatient because after that last miscarriage it lasted one and a half year before we were pregnant again. So I thought it would take one and a half year again to become pregnant so we tried again a month after the miscarriage". [34-3]

Coping

"What always amazed me is that they [healthcare workers] do not talk about it [duration conception time] and especially when it takes a while before you get pregnant…… However, that phase between I considered useless in the hospital, due to the fact that I though you (health care workers) could give me some advice about at least the good moments, the ovulations. Of course you can search internet or in books but it would have been nice to talk about it and to have some advice". [34-3]

UMC Utrecht

Searching for control

Emotions

"And the whole society is so constituted that you should have control over everything and I think that's the big ..... that is what makes it so difficult for many people. And you just have no grip on it". [33-2]

Coping

"I [experience] less that it…lives in me….a word [lives] that I will not use soon…I do not allow that thought ……at [a] distance…that picture … that little heart…with arms and legs and body so beautiful that you can see…I have experienced as traumatic…..

if it goes wrong …….so that is why I do not see it as a living creature….I do not want contact with it……" [32-3]

UMC Utrecht

Balancing between loss of control and searching for control

Loss of control

- Number of miscarriages
- Mixed feelings
- Goal "having a child"

Searching for control

Observing strategies

- Pregnancy symptoms
- Pregnancy tests
- Ultra sounds

Controlling strategies

- Lifestyle adaptations
- Bracing strategies

UMC Utrecht

Results use of the PRCI and DRK

Theme's

- Adapted use of PRCI
- Adapted use of DRK
- Practicality and feasibility of the PRCI and the DRK

UMC Utrecht

Conclusion

- Women are in need of support during waiting periods
- PRCI can be offered for waiting periods
- Women adapt the use of interventions
- More RCT's have to be done to investigate effectiveness other populations

UMC Utrecht

Supporting women during waiting periods

Hetty Ockhuijsen
H.D.L.Ockhuysen@umcutrecht.nl

UMC Utrecht

References

- Boivin J and Lancastle D. Medical waiting periods: imminence, emotions and coping. Womens Health (Lond Engl) 2010:6:59-69.
- Fogarty C and Cronin P. Waiting for healthcare: a concept analysis. J Adv Nurs 2008:61:463-471.
- Folkman S. The case for positive emotions in the stress process. Anxiety Stress Coping 2008:21:3-14.
- Folkman S. Positive psychological states and coping with severe stress. Soc Sci Med 1997:45:1207-1221.
- Lazarus RS. Stress, appraisal, and coping / Richard S. Lazarus, Susan Folkman. 1984. Springer Pub. Co, New York :.
- Ockhuijsen HD, Boivin J, van den Hoogen A and Macklon NS. Coping after recurrent miscarriage: uncertainty and bracing for the worst. J Fam Plann Reprod Health Care 2013:39:250-256.

UMC Utrecht

Decision aids on the type of medication: An interactive session

Eline Dancet
RM, Msc, PhD

Academic Medical Centre, The Netherlands;
Leuven University, Belgium

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

No conflict of interest

Only co-applicant of unrestricted research grant from a pharmaceutical company

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Learning objectives (1)

Informed shared decision-making and decision-aids

- Why informed, shared patient-physician decision-making?
- What are the steps in informed, shared patient-physician decision-making?
- Why consider using decision aids?
- Available decision aids?

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Learning objectives (2)

The choice for hormonal fertility medication

- Which choices are made in clinical practice?
- Which medication aspects to take into account according to patients?
- Three decision aids for the choice of hormonal fertility medication
- Pilot tests among patients and physicians
- Ungoing efforts to improve the decision aids
- **Using the three decision aids**

Informed, shared decision-making and decision aids

Why informed, shared patient-physician decision-making? (1)

- **Current clinical practice decision-making**:
  -> **professionals**
  based on patients' physical condition
- **Patients' experiences** with informed, shared decision-making **are problematic**

(Culley et al, 2006; Dancet et al, 2010; Dancet et al, 2014;Haagen et al, 2008; Hammarbergh et al, 2001;Morrison et al, 2007, Peddie et al, 2004, Sabourin et al, 1991, Schmidt et al. 2003, Souter et al, 1998; Ludwig et al, 2005; Dancet et al, 2010; van Empel et al, 2010)

Why **informed**, shared patient-physician decision-making? (2)

- **Subfertile patients value:**
  - general information
  - personalized information
  - professionals taking time for answering questions

⇨ worth almost 10% of IVF-pregnancy rate

(Dancet et al, 2010; Dancet et al 2011; Dancet et al, 2012; Leite et al, 2005; Peddie et al, 2005; Schmidt,1998; Souter et al. 1998;van Empel et al, 2010)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Why **informed**, shared patient-physician decision-making? (3)

'Because we thaught, some hormones and hoera, after half a year we succeed. *But that was wrong. No one spoke about success rates or treatment trajectories You have no clue about what is happening to you and therefore do not know which questions to ask.*' (FG, the Netherlands)

(Dancet et al 2011)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Why informed, **shared** patient-physician decision-making? (4)

- **Subfertile patients value:**
  - being involved in treatment decision-making
  (> older or seriously ill patients;
  involve couple rather than one patient)
  - If not involved, couple: feels loss of control
  perceives care as less patient-centered

⇨ worth changing clinics for

(Charles et al, 1998; Blenner,1990; Stewart et al, 2001a; Dancet et al, 2010; Dancet et al 2011; Dancet et al, 2012; Rauprich et al., 2011; ; Sol Olafsdottir, 2013; van Empel et al, 2010; van Empel et al, 2011)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Why informed, **shared** patient-physician decision-making? (5)

'*The second most important to me, is patient involvement in medical decision-making. That is very important to me. That as a patient, you are involved in the team and the process of thaugths and can join in the decision-making'* (FGG, BE)

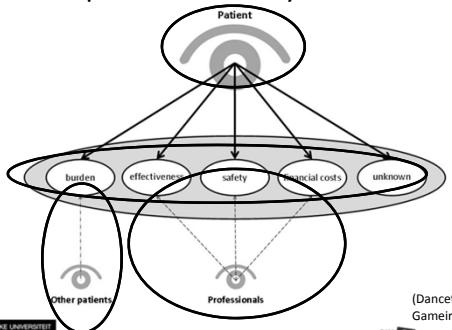
(Dancet et al 2011)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Why informed, shared patient-physician decision-making? (4)

Framework for patient-centered fertility treatment



(Dancet et al, 2014; Gameiro et al, 2013)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

What are the steps in informed, shared patient-physician decision-making?

1) **Team talk:** explain that the optimal choice depends on what matters most to the individual patient;
2) **Option talk:** inform patients on the (dis)advantages of each option;
3) **Decision talk:** decide together with the individual patient on his/her optimal option

(Mulley et al, 2012; Sol Olafsdottir, 2013)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Why consider using decision aids? (1)

- **DAs**:
  - provide **evidence-based information**
  - acknowledge the **importance of individual values**
  - **structure** the decision-making process and communication
  - result in **specific, thought-out choices between options**
- **Types:**
  - Long: booklet, information brochure, webpage *Prior*
  - Short: Decision boards, option grids ***(new!)*** *During*

⇒ **Facilitate team talk, option talk, decision talk**

(Elwyn et al, 2006; Stacey et al, 2011)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Why consider using decision aids? (2)

ADVANTAGES:

- Affects choices
- For patients: less anxiety, more knowledge, more 'values-based choices' , less decisional conflict
- For professionals: better communication with patients, more patient-centered care
- Variabel effect on consultation duration

(Stacey et al, 2011)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Available decision aids?

AVAILABLE:

- **Other fields:** DAs for screenings and treatment decisions
  30 (2003) → 56 (2009) → 86 (2011)
- **Fertility:** - Number of embryo's to transfer
  - Fertility preservation among female cancer patients
  - Hormonal fertility medication

(Peate et al, 2012; Stacey et al, 2011; van Peperstraten et al, 2010 a-b)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

The choice for hormonal fertility medication

Which choices are made in clinical practice? (1)

Three medication phases of IVF-treatments:

- induction of pituitary quiescence
- ovarian stimulation
- luteal support

For which available medications differ in:

- route of administration (e.g. vaginal or oral)
- application form (e.g. cartridge pen or pre-filled pen)
- dosage regimen (e.g. daily or weekly depot)
- required self-administration skills (e.g. self-preparation or not)

Which choices are made in clinical practice? (2)

Induction of pituitary quiescence

- Suprefact® (nasal/ spray/ 3x or 4x per day/ self-application via nose)
- Decapeptyl® (SC injection/ prefilled syringe with attached needle/ 1x per day/ self-injection subcutaneously)
- Elonva® (SC injection/ prefilled syringe with attached need/ 1x per day/ injection by health care professional)
- …

Which choices are made in clinical practice? (3)

Ovarian stimulation

- Menopur® (SC injection/ syringe + needle + ampula water and powder/ 1x per day/ self-preparation and self-injection subcutaneously)
- Puregon® (SC injection/ cartridge pen + needle / 1x per day/ self-injection subcutaneously)
- Gonal-F® (SC injection/ prefilled pen + needle / 1x per day/ self-injection subcutaneously)
- Elonva® (SC injection/ prefilled syringe with attached need/ 1x per day/ injection by health care professional)
- ...

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Which choices are made in clinical practice? (4)

Luteal support

- Utrogestan® (vaginal/ ovulas/ 3x per day/ self-application vwith or without reusable apllicator)
- Crinone® vaginal/ gel in apllicator/ 2x per day/ self-application with apllicator)
- Pregnyl® (SC injection/ syringe + needle + ampula water and ampula powder/ 1x per day/ self-preparation and self-injection subcutaneously)
- ....

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Which medication aspects to take into account according to patients? (1)

- Data-collection: in-depth individual interviews with 20 fertility patients from Belgium or the Netherlands
- Focus: Patients' experiences with medication and medication aspects so important that they could define their choice
- Analysis: transcription and content analysis

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Which medication aspects to take into account according to patients? (2)

16 Frequently asked questions (part I)

- Does the chance of becoming pregnant differ between medications?
- How does the medication work?
- What is the route of administration?
- What is the frequency and timing of administration?

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Which medication aspects to take into account according to patients? (3)

16 Frequently asked questions (part II)

- Is duly administration at strictly fixed points in time important?
- Is the medication ready-made for administration?
- Can I learn to prepare and administer the medication myself?
- Could the preparation of the medication cause concerns?

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Which medication aspects to take into account according to patients? (4)

16 Frequently asked questions (part III)

- Could the administration of the medication cause concerns?
- Could the medication cause psychological side effects?
- Could the medication cause general side effects?
- Could the medication cause local side effects?

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Which medication aspects to take into account according to patients? (5)

16 Frequently asked questions (part IV)

- How much will the medication cost me or the society per cycle?
- *Can I take the medication with me and administer it during an outdoor work or social event, without attracting attention to my fertility problem and treatment?*
- *What are the practical requirements for storage and disposal?*
- *Can I involve my partner in preparing and administrating the medication?*

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

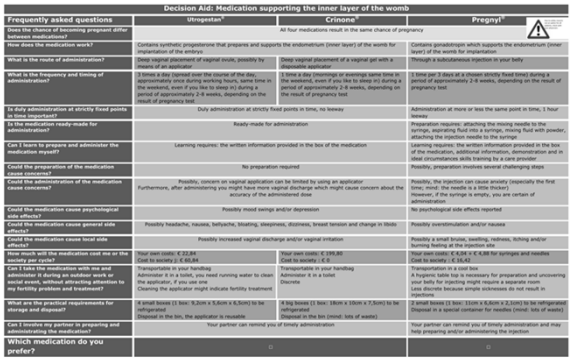
Three decision aids for the choice of hormonal fertility medication (1)

Decision Aid: Medication to suppress your hormonal cycle		
Frequently asked questions	**Suprefact®**	**Decapeptyl®**
Does the chance of becoming pregnant differ between medications?	Both medications result in the same chance of pregnancy	
How does the medication work?	Contains gonadotropin releasing hormone-agonists that prevent the production of gonadotropins (female hormones) by the hypofyse (an organ in the brain), which in turn prevents untimely ovulation	
What is the route of administration?	Through your nose (nasal spray)	Through a subcutaneous injection in your belly
What is the frequency and timing of administration?	3 or 4 times a day (spread over the course of the day, approx. 1 or 2 times during working hours, same time in the weekend, even if you like to sleep in) during a period of approx. 3 to 4 weeks.	1 time a day (at a freely chosen moment in the evening) during a period of approx. 3 to 4 weeks.
Is duly administration at strictly fixed points in time important?	Duly administration at strictly fixed points in time, no leeway.	Administration at more or less the same point in time, 1 hour leeway
Is the medication ready-made for administration?	Ready-made for administration	
Can I learn to prepare and administer the medication myself?	Learning requires: the written information provided in the box of the medication	Learning requires: the written information provided in the box of the medication, additional information, demonstration and in ideal circumstances skills training by a care provider
Could the preparation of the medication cause concerns?	Concerns are unlikely	
Could the administration of the medication cause concerns?	Possibly if you have a cold. Otherwise, you will feel the medication run up your nose, which reassures you of administration	Possibly, the injection can cause anxiety (especially the first time) although the needle is quite short and thin. However, when the syringe is empty you are certain of administration
Could the medication cause psychological side effects?	Possibly mood swings	
Could the medication cause general side effects?	Possibly: hot flashes, vaginal blood loss, headache, fatigue, sleeping problems, dizziness, bellyache, nausea, vomiting and /or loss of libido	
Could the medication cause local side effects?	Possibly: Irritation of the nasal mucosa	Possibly: a bruise and/or a burning feeling at the injecting site
How much will the medication cost me or the society per cycle?	Your own cost: 0 euro Cost to society: 147,46 euro	Your own cost: 0 euro Cost to society: 168,56 euro
Can I take the medication with me and administer it during an outdoor work or social event, without attracting attention to my fertility problem and treatment?	*Transportable in your handbag* *No special requirements for the space where you administer* *Discrete because a nose spray could be used for a simple cold*	*Transportation in a cool box* *Uncovering your belly for injecting might require a separate room* *Less discrete because simple sicknesses do not result in injections*
What are the practical requirements for storage and disposal?	*One big box (16,8cm x 11,9cm x 7,4cm) to be kept refrigerated In the bin, limited amount of waste*	*4 big boxes (1 box: 15,5cm x 15,2cm x 3cm) to be kept refrigerated* *In a special needle container, more waste*
Can I involve my partner in preparing and administrating the medication?	*Your partner can remind of timely administration*	*Your partner can remind of timely administration and some couples choose for the partner to administrate the injection*
Which medication do you prefer?	□	□

Three decision aids for the choice of hormonal fertility medication (2)

Decision Aid: Medication for stimulating the maturation of multiple egg cells				
Frequently asked questions	**Menopur®**	**Puregon®**	**Gonal-F®**	**Elonva®** (+potential additional Puregon® injections)
Does the chance of becoming pregnant differ between medications?	All four medications result in the same chance of pregnancy			
How does the medication work?	Contains human menopausal gonadotropin that stimulates the maturation of multiple egg cells	Contains a synthetic form of a follicle stimulating hormone (FSH) that stimulates the maturation of multiple egg cells		
What is the route of administration?	Through a subcutaneous injection in your belly			
What is the frequency and timing of administration?	1 time per day at a freely chosen moment in the evening during a period of approximately 12 days			Elonva® is a one-time injection working for 7 days
Is duly administration at strictly fixed points in time important?	Daily administered at more or less the same point in time, 1 hour leeway			It is a one-time injection
Is the medication ready-made for administration?	Preparation requires: calculating the amount of bottles required for the prescribed dose of medication, attaching the mixing needle to the first go, aspirating fluid into a syringe, mixing a fluid with powder, attaching the injection needle to the syringe	Preparation requires: placing a cartridge in the pen, attaching a needle to the pen, marking the prescribed dose on the pen	Preparation requires: attaching a needle to the pen, marking the prescribed dose on the pen	The medication is ready-made for administration
Can I learn to prepare and administer the medication myself?	Learning requires: the written information provided in the box of the medication, additional information, demonstration and in ideal circumstances skills training by a care provider			
Could the preparation of the medication cause concerns?	Possibly, preparation involves several challenging steps	Possibly, preparation of the injection pen and adjusting the dose can cause concern		Concerns are unlikely
Could the administration of the medication cause concerns?	Possibly, the injection can cause anxiety (especially the first time). mind: the needle is a little thicker. However, if the syringe is empty, you are certain of administration	Possibly, the injection can cause anxiety (especially the first time), although he needle quite short and thin. Furthermore, after administering the pen is not empty, which might cause . concern about the accuracy of the administered dose.		Possibly, the injection can cause anxiety (especially the first time) although the needle is quite short and thin. However, if the syringe is empty, you are certain of administration
Could the medication cause psychological side effects?	No psychological side effects reported			
Could the medication cause general side effects?	Possibly headache, abdominal ache, nausea, bloating, gain of weight, pain in the pelvis and/or overstimulation			The same side effects and additionally possibly dizziness, breast tension and/or fatigue.
Could the medication cause local side effects?	Possibly a small bruise, swelling, redness, itching, pain and/or burning feeling at the injection site			
How much will the medication cost me or the society per cycle?	Your own costs: € 4,88 for syringes and needles Cost to society: 778,64 euro	Your own costs: € 0 euro Cost to society: € 960,42	Your own costs: € 0 Cost to society: € 1059,21	Your own costs: € 0 Cost to society: € 577
Can I take the medication with me and administer it during an outdoor work or social event, without attracting attention to my fertility problem and treatment?	Transportation in your handbag (quite a bulk for Menopur®, a case is provided for Puregon®) A hygienic table top is necessary for preparation and uncovering your belly injecting might require a separate room Attracting attention to your fertility is likely because simple sicknesses do not result in injections			
What are the practical requirements for storage and disposal?	4 small boxes (1 box: 12,2cm x 11cm x 4,4cm) to be stored at room temperature; Disposal in a special container for needles (immd. bits of waste)	3 to 9 small boxes (1 box: 9,5cm x 6,5cm x 4cm) to be refrigerated; Disposal in a special container for needles, the pen is reusable	3 to 9 big boxes (1 box: 20,2cm x 9,8cm x 3,4cm) to be refrigerated; Disposal in a special container for needles, the pen can be recycled	One big box (17,2cm x 7,1cm x 3,6cm) to be refrigerated; Disposal in a special container for needles, (immd. little waste)
Can I involve my partner in preparing and administrating the medication?	Your partner can remind you of timely administration and may help preparing and/or administering the injection			
Which medication do you prefer?	□	□	□	

Three decision aids for the choice of hormonal fertility medication (3)



Decision Aid: Medication supporting the inner layer of the womb

Frequently asked questions	Utrogestan®	Crinone®	Pregnyl®
Does the chance of becoming pregnant differ between medications?	All four medications result in the same chance of pregnancy		
How does the medication work?	Contains synthetic progesterone that prepares and supports the endometrium (inner layer) of the womb for implantation of the embryo		Contains gonadotropin which supports the endometrium (inner layer) of the womb for implantation
What is the route of administration?	Deep vaginal placement of vaginal ovule, possibly by means of an applicator	Deep vaginal placement of a vaginal gel with a disposable applicator	Through a subcutaneous injection in your belly
What is the frequency and timing of administration?	3 times a day (spread over the course of the day, approximately once during working hours, same time in the weekend, even if you like to sleep in) during a period of approximately 2-8 weeks, depending on the result of pregnancy test	1 time a day (mornings or evenings same time in the weekend, even if you like to sleep in) during a period of approximately 2-8 weeks, depending on the result of pregnancy test	1 time per 2 days at a chosen strictly fixed time) during a period of approximately 2-8 weeks, depending on the result of pregnancy test
Is duly administration at strictly fixed points in time important?	Duly administration at strictly fixed points in time, no leeway		Administration at more or less the same point in time, 1 hour leeway
Is the medication ready-made for administration?	Ready-made for administration		Preparation requires: attaching the mixing needle to the syringe, aspirating fluid into a syringe, mixing fluid with powder, attaching the injection needle to the syringe
Can I learn to prepare and administer the medication myself?	Learning requires: the written information provided in the box of the medication		Learning requires: the written information provided in the box of the medication, additional information, demonstration and in ideal circumstances skills training by a care provider
Could the preparation of the medication cause stress?	No preparation required		Possibly, preparation involves several challenging steps
Could the administration of the medication cause concerns?	Possibly, concern on vaginal application can be limited by using an applicator Furthermore, after administering you might have more vaginal discharge which might cause concern about the accuracy of the administered dose		Possibly, the injection can cause anxiety (especially the first time; mind: the needle is a little thicker) However, if the syringe is empty, you are certain of administration
Could the medication cause psychological side effects?	Possibly mood swings and/or depression		No psychological side effects reported
Could the medication cause general side effects?	Possibly headache, nausea, bellyache, bloating, sleepiness, dizziness, breast tension and change in libido		Possibly overstimulation and/or nausea
Could the medication cause local side effects?	Possibly increased vaginal discharge and/or vaginal irritation		Possibly a small bruise, swelling, redness, itching and/or burning feeling at the injection site
How much will the medication cost me or the society per cycle?	Your own costs: € 22,84 Cost to society ≥ € 60,84	Your own costs: € 199,80 Cost to society : € 0	Your own costs: € 4,06 + € 4,88 for syringes and needles Cost to society : € 10,42
Can I take the medication with me and administer it during an outdoor work or social event, without attracting attention to my fertility problem and treatment?	Transportable in your handbag Administer it in a toilet, you need running water to clean the applicator, if you use one Cleaning the applicator might indicate fertility treatment	Transportable in your handbag Administer it in a toilet Discrete	Transportation in a cool box A hygienic table top is necessary for preparation and uncovering your belly for injecting might require a separate room Less discrete because simple sicknesses do not result in injections
What are the practical requirements for storage and disposal?	4 small boxes (1 box: 9,2cm x 5,6cm x 6,5cm) to be refrigerated Disposal in the bin, the applicator is reusable	4 big boxes (1 box: 18cm x 10cm x 7,5cm) to be refrigerated Disposal in the bin (mind: lots of waste)	2 small boxes (1 box: 11cm x 6,6cm x 2,1cm) to be refrigerated Disposal in a special container for needles (mind: lots of waste)
Can I involve my partner in preparing and administrating the medication?	Your partner can remind you of timely administration		Your partner can remind you of timely administration and may help preparing and/or administering the injection
Which medication do you prefer?	□		□

Pilot test among patients and physicians (1)

Twenty IVF-patients:

- Clear and intelligible
- Right amount of frequently asked questions and information,
- Table format appropriate.

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Pilot test among patients and physicians (2)

Twenty IVF-patients:

- Twenty-five comments:
  - clarity (e.g. side effects) ⇒ reformulation
  - terminology (e.g. ovarian)
  - *content (e.g. many medications)* ⇒ reorganizing
  - order of frequently asked questions
  - graphic design (e.g. recognizing medication) ⇒ Pictures, names
  - *conditions for usability (e.g. practical skills demonstration)*

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Pilot test among patients and physicians (3)

Five gynecologists

- Enthusiast about dense summary of information
- Would prefer shorter but all relevant FAQs
- Indicate that Elonva® and Pregnyl® could for safety reasons only prescribed under certain conditions

⇒ Willing to use the option grids in daily practice, if the option grids read in advance by patients

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Ungoing efforts to improve the decision aids

- Exploring whether they can be shortened
- Testing the effect on various outcomes (values-based choice, choice, knowledge, anxiety)
- Testing the feasibility of using them in clinical practice

Using the three decision aids (1)

Steps of informed, shared decision-making

1) **Team talk:** explain that the optimal choice depends on what matters most to the individual couple ⇒ **FAQs**
2) **Option talk:** inform patients on the (dis)advantages of each option ⇒ **Answers to FAQs**
3) **Decision talk:** decide together with the individual patient on his/her optimal option ⇒ **Mark choice**

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Using the three decision aids (2)

Practice

- Groups of 4
  - couple (n=2)
  - health care professional (n=1)
  - observer (n=1)
- Take 7 minutes for shared decision-making, switch places (x3)

(Lankreijer et al, in preparation)

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

Using the three decision aids (3)

Feedback?

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

References (1)

- Blenner JL. Attaining self-care in infertility treatment. Appl Nurs Res 1990 : 3(3); 98-104.
- Charles C, Redko C, Whelan T, Gafni A, Reyno L. Doing Nothing is No Choice: Lay Constructions of Treatment Decision-making Among Women with Early-stage Breast Cancer. Social Health Illness 1998; 20:71-95.
- Culley LA, Hudson N, Rapport FL, Katbamna S, Johnson MRD. British South Asian communities and infertility services. Hum Fertil (Camb) 2006 : 9(1); 37-45.
- Dancet EA, Nelen WL, Sermeus W, De Leeuw L, Kremer JA, D'Hooghe TM. The patients' perspective on fertility care: a systematic review. Hum Reprod Update. 2010; 16(5):467-87.
- Dancet EA, Van Empel IW, Rober P, Nelen WL, Kremer JA, D'Hooghe TM. Patient-centred infertility care: a qualitative study to listen to the patient's voice. Hum Reprod. 2011; 26(4):827-33.

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

References (2)

- Dancet EA, D'Hooghe TM, Sermeus W, van Empel I, Strohmer H, Wyns C, Santa-Cruz D, Nardo LG, Kovatchki D, Vanlangenakker L, Garcia-Velasco J, Mulugeta B, Nelen WL, Kremer JA. Patients from across Europe have similar views on patient-centred care: an international multilingual qualitative study in infertility care. Hum Reprod. 2012; 27(6):1702-11.
- Dancet EA, D'Hooghe TM, van der Veen F, Bossuyt P, Sermeus W, Mol BW, Repping S. "Patient-centered fertility treatment": what is required? Fertil Steril. 2014; 101(4):924-6.
- Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, Thomson R,Barratt A, Barry M, Bernstein S, Butow P, Clarke A, Entwistle V, Feldman-Stewart D, Holmes-Rovner M, Llewellyn-Thomas H, Moumjid N, Mulley A, Ruland C, Sepucha K, Sykes A, Whelan T; International Patient Decision Aids Standards (IPDAS) Collaboration. Developing a quality criteria framework for patient decision aids:online international Delphi consensus process. BMJ. 2006;333(7565):417.

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

References (3)

- Gameiro S, Boivin J, Domar A. Optimal in vitro fertilization in 2020 should reduce treatment burden and enhance care delivery for patients and staff. Fertil Steril. 2013; 100(2):302-9.
- Haagen EC, Hermens RP, Nelen WL, Braat DD, Kremer J, Grol R. Subfertile couples' negative experiences with intrauterine insemination care. Fertil Steril 2008 : 89(4); 809-16.
- Hammarbergh K, Astbury J, Baker HWG. Women's experience of IVF: a follow-up study. Hum Reprod 2001 : 16(2); 374-83.
- Leite RC, Makuck MY, Petta CA, Morais SS. Women's satisfaction with physicians' communication skills during an infertility consultation. Patient Educ Couns 2005: 59(1); 38-45 .
- Lankreijer, Dancet et al. Decision aids to involve patients in chosing hormonal fertility medication, in preparation.
- Ludwig AK, Diedrich K, Ludwig M. The process of decision making in reproductive medicine. Semin Reprod Med. 2005;23:348-53.
- Morrison C, Bhattacharya S, Hamilton M, Templeton A, Smith B. Initial management of infertility: an audit of pre-referral investigations and exploration of couples' views at the interface of primary and secondary care. Hum Fertil (Camb) 2007 :10(1); 25-31.
- Mulley AG, Trimble C, Elwyn G. Stop the silent misdiagnosis: patients' preferences matter. BMJ. 2012; 8;345:e6572.

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

References (4)

- Peate M, Meiser B, Cheah BC, Saunders C, Butow P, Thewes B, Hart R, Phillips KA, Hickey M, Friedlander M. Making hard choices easier: a prospective, multicentre study to assess the efficacy of a fertility-related decision aid in young women with early-stage breast cancer. Br J Cancer. 2012 Mar 13;106(6):1053-61. doi: 10.1038/bjc.2012.61.
- Peddie VL, van Teijlingen E, Bhattacjarya S. Ending in-vitro fertilization: women's perception's of decision making. Hum Fertil (Camb) 2004 : 7(1); 31-7.
- Peddie VL, van Teijlingen E, Bhattacharya S. A qualitative study of women's decision-making at the end of IVF treatment. *Hum Reprod.* 2005;**20**:1944-51.
- Rauprich O, Berns E, Vollmann J. Information provision and decision-making in assisted reproduction treatment: results from a survey in Germany. Hum Reprod. 2011;26:2382-91
- Sabourin S, Wright J, Duchesne C, Belisle S. Are consumers of modern fertility treatments satisfied? Fertil Steril 1991 : 56(6); 1084-90.

KATHOLIEKE UNIVERSITEIT LEUVEN

am center for reproductive medicine

References (5)

- Schmidt L. Infertile couples' assessment of infertility treatment. Acta Obstet Gynecol Scand 1998 : 77(6); 649-53.
- Schmidt L, Holstein BE, Boivin J, Tjornhoj-Thomsen T, Blaabjerg J, Hald F, Rasmusser PER, Nyboe Andersen A. High ratings of satisfaction with fertility treatment are common: findings from the Copenhagen Multi-centre Psychosocial Infertility (COMPI) Research Programme.Hum Reprod 2003 : 18(12); 2638-46.
- Sol Olafsdottir H, Wikland M, Möller A. Nordic couples' decision-making processes during assisted reproduction treatments. Sex Reprod Healthc. 2013;4(2):49-55.
- Souter VL, Penney G, Hopton JL, Templeton AA. Patient satisfaction with the management of infertility. Hum Reprod 1998 : 13(7); 1831-6.
- Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Légaré F, Thomson R. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2011;(10):CD001431. doi: 10.1002/14651858.CD001431.pub3. Review. Update in: Cochrane Database Syst Rev. 2014;1:CD001431.
- Stewart DE, Rosen B, Irvine J, Ritvo P, Shapiro H, Murphy J, Thomas J, Robinson GE, Neuman J, Deber DR. The disconnect: infertility patients' information and the role they wish to play in decision making. Medscape Womens Health 2001 : 6(4); 1 .

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

References (6)

- van Empel IW, Aarts JW, Cohlen BJ, Huppelschoten DA, Laven JS, Nelen WL, Kremer JA. Measuring patient-centredness, the neglected outcome in fertility care: a random multicentre validation study. Hum Reprod. 2010; 25(10):2516-26.
- van Empel IW, Dancet EA, Koolman XH, Nelen WL, Stolk EA, Sermeus W, D'Hooghe TM, Kremer JA. Physicians underestimate the importance of patient-centredness to patients: a discrete choice experiment in fertility care. Hum Reprod. 2011; 26(3):584-93.
- van Peperstraten AM, Hermens RP, Nelen WL, Stalmeier PF, Wetzels AM, Maas PH, Kremer JA, Grol RP. Deciding how many embryos to transfer after in vitrofertilisation: development and pilot test of a decision aid. Patient Educ Couns. 2010a;78(1):124-9.
- Van Peperstraten A, Nelen W, Grol R, Zielhuis G, Adang E, Stalmeier P, Hermens R, Kremer J. The effect of a multifaceted empowerment strategy on decision making about the number of embryos transferred in in vitro fertilisation: randomised controlled trial. BMJ. 2010b;341:c2501.

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

Thank you for your attention!

e.a.dancet@amc.uva.nl

KATHOLIEKE UNIVERSITEIT LEUVEN

amc center for reproductive medicine

The fine line of support and pressure - The role of family and friends.

Dr. Helga Sól Ólafsdóttir
Social worker/ counselor
Dept. obst.gyn. Univ.hospital of Iceland
Art Medica

eshre Annual Meeting MUNICH, Germany 29 June to 2 July 2014

I declare that I have no commercial or financial interestes pertaining to the subject of this presentation or its content.

eshre Annual Meeting MUNICH, Germany 29 June to 2 July 2014

Objective of presentation

People are not isolated. They have family and friends that they can turn to for help, that cry for them and with theim, give good and bad advice, love them and get them crazy all in one day!

- What is the role of family and friends towards persons or couples dealing with infertility?
- When is a relationship supportive or pressuring?
- Why is this knowledge important for us?

UPCOMING ESHRE EVENTS

// ESHRE CAMPUS EVENTS

ESHRE's 30th Annual Meeting

www.eshre2014.eu

Munich, Germany
29 June - 2 July 2014

Epigenetics in reproduction

www.eshre.eu/lisbon

Lisbon, Portugal
26-27 September 2014

Endoscopy in reproductive medicine

www.eshre.eu/endoscopyoct

Leuven, Belgium
15-17 October 2014

Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering **www.eshre.eu/thessaloniki**

Thessaloniki, Greece
31 October-1 November 2014

From gametes to blastocysts – a continuous dialogue

www.eshre.eu/dundee

Dundee, United Kingdom
7-8 November 2014

Controversies in endometriosis and adenomyosis

www.eshre.eu/liege

Liège, Belgium
4-6 December 2014

Bringing evidence based early pregnancy care to your clinic

www.eshre.eu/copenhagen

Copenhagen, Denmark
11-12 December 2014

An update on preimplantation genetic screening (PGS)

www.eshre.eu/rome

Rome, Italy
12-13 March 2014

For information and registration: www.eshre.eu/calendar
or contact us at info@eshre.eu

eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES