Centrum voor Voortplantingsgeneeskunde amc

Recurrent Miscarriage: definition issues

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E. van den Boogaard

ESHRE Campus, Rotterdam dec 2009

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Recurrent Miscarriage: definition issues

- Background
  - Recurrent miscarriage work up
  - Guidelines

- Two versus three or more miscarriages
- Maternal Age
- Consecutive versus non-consecutive
- Conclusions

Definition Recurrent Miscarriage

- Good Clinical Practice starts with a clear definition of the clinical problem
- Definitions vary
  - Country
  - Professional Association (ESHRE/RCOG/ACOG)
- No consensus with regard to
  - Number of preceding miscarriages
  - Gestational age of miscarriages
  - Consecutive vs non-consecutive miscarriages

Definition Recurrent Miscarriage

ACOG	2001:	≥ 2 consecutive miscarriages < 15 weeks GA
RCOG	2003:	≥ 3 miscarriages
ESHRE	2006:	≥ 3 consecutive miscarriages < 20 weeks GA
NVOG	2007:	≥ 2 miscarriages < 20 weeks GA

ACOG
THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

eshre
science moving people moving science

Royal College of Obstetricians and Gynaecologists
Setting standards to improve women's health

nvog
NEDERLANDSE VERENIGING VOOR OBSTETRIE & GYNAECOLOGIE

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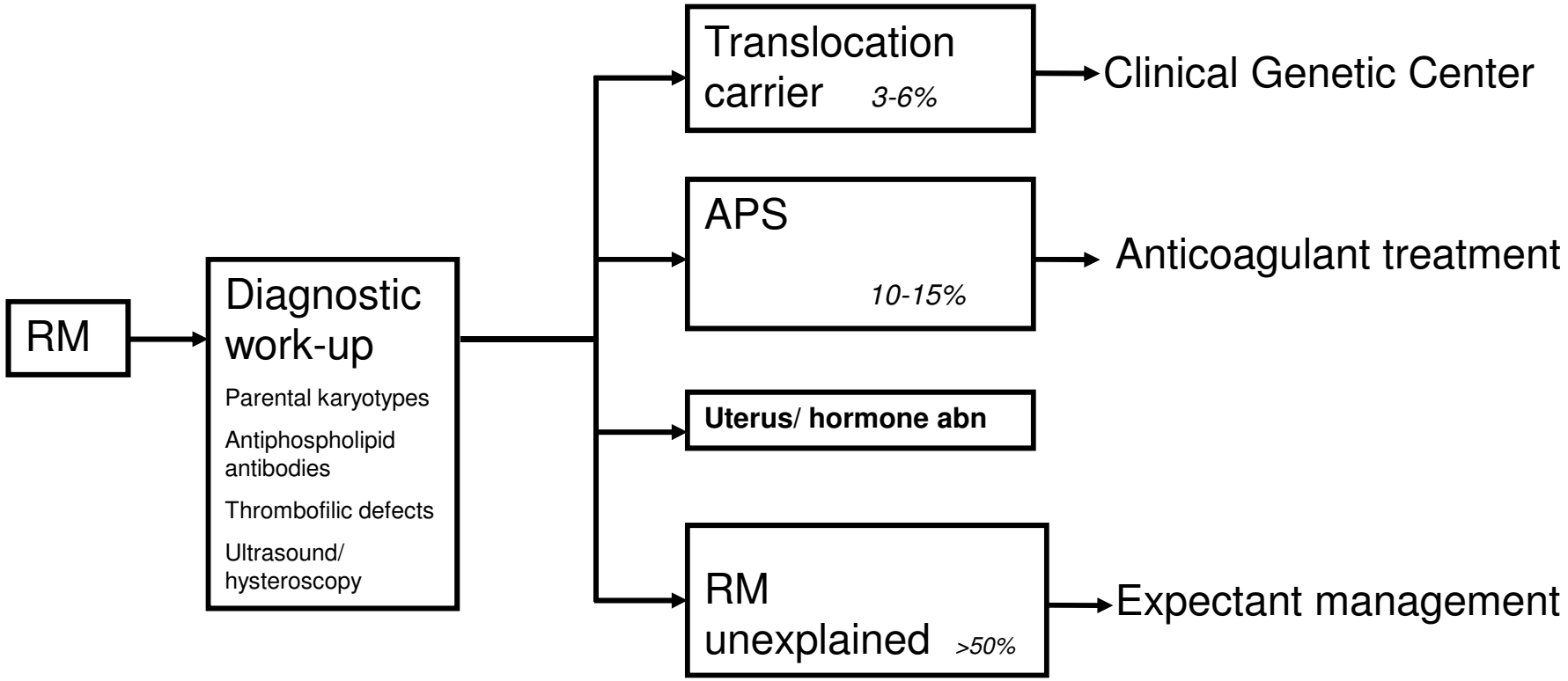
Recurrent miscarriage work-up



All couples: advise healthy life style

Recurrent miscarriage work-up

Advice[1]

- favour evidence based management
- promote Randomised Controlled Trials

Practice[2]

- too many diagnostic tests and ineffective interventions performed
- adherence to the guideline Recurrent Miscarriage rather poor

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[1]Rai Lancet 2006, [2]Franssen Hum Reprod 2007

Definition evidence

- Absence of evidence
  - Definition is not a topic of research
- Try to define RM using data instead of discussions
  - 2 vs 3
  - Role of maternal age
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Selective karyotyping

- Maternal age is a the strongest risk factor for a structural chromosome abnormality
- The higher maternal age the lower the chance of a structural chromosome abnormality
- Other factors contributing to the risk:
  - History of ≥ 3 miscarriages vs 2 miscarriages
  - History of ≥ 2 miscarriages in a brother or sister
  - History of ≥ 2 miscarriages in a parent

6 centres for clinical genetics
279 carrier couples
428 non-carrier couples

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Franssen BMJ 2005

Selective karyotyping

Maternal age (years) at second miscarriage		RM parents +		RM parents -	
		≥3 misc.	2 misc.	≥3 misc.	2 misc.
< 23	RMbs +	**10.2%**	**7.3%**	**7.3%**	**5.2%**
	RMbs -	**5.7%**	**4.0%**	**4.1%**	**2.8%**
23-34	RMbs +	**10.0%**	**7.2%**	**7.2%**	**5.1%**
	RMbs -	**5.7%**	**4.0%**	**4.0%**	**2.8%**
34-37	RMbs +	**5.8%**	**4.1%**	**4.1%**	**2.9%**
	RMbs -	**3.2%**	**2.2%**	**2.2%**	**1.6%**
37-39	RMbs +	**4.0%**	**2.8%**	**2.8%**	**2.0%**
	RMbs -	**2.2%**	**1.5%**	**1.5%**	**1.1%**
≥ 39	RMbs +	**1.8%**	**1.2%**	**1.3%**	**0.9%**
	RMbs -	**1.0%**	**0.7%**	**0.7%**	**0.5%**

Adopted in guidelines: ESHRE 06, NVOG 07

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Franssen BMJ 2005

Pregnancy outcome RM unexplained

Success rate (≥ 24 weeks)

Number of miscarriages →

Female age ↓

N=222	2	3	4	5
25	89	86	82	79
30	84	80	76	71
35	77	73	68	62
40	69	64	58	52
45	60	54	48	42

Overall 75% chance of a successful pregnancy

Brigham Hum Rep 1999

Pregnancy outcome RM unexplained

- The higher maternal age, and the higher the number of preceding miscarriages, the lower the chance of success
- Maternal age is a stronger risk factor when compared to number of miscarriages
- Maternal age is not taken into account in any definition

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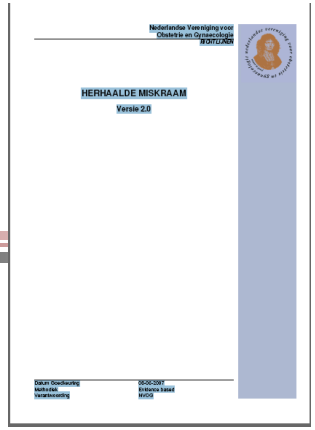
Brigham Hum Rep 1999

Dutch Guideline (NVOG) 2007



	Do	Don't	Evidence Level
PGS		X	No RCTs
PGD (indication of structural chromosome abnormality in male or female partner)	?*		No RCTs
Progesterone or hCG		X	B
Correction of uterine anomaly		X	No RCTs
Anticoagulant treatment (indication antiphospholipid syndrome)	X		B
Anticoagulant treatment (indication hereditary thrombophilia factor)		X	B
Advise to lose weight	X		B
Stop smoking	X		B
Eat healthily	X		C
Calculate prognosis for subsequent pregnancy (if unexplained recurrent miscarriage)	X		B

NVOG guideline Recurrent Miscarriage 2007
translation: NGC website www.guideline.gov

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ALERT implementation study

- Retrospective cohort study
- 9 departments of Obstetrics and Gynaecology in The Netherlands
- Patients with recurrent miscarriage in 2006
- Hospital financial registries (≥1 miscarriage) and centers for Clinical Genetics
- Medical charts and patient questionnaires

ALERT implementation study

- Measurement of actual care
- Identify barriers and facilitators
- Develop a strategy for improvement

ALERT

UMC St Radboud

TNO | Kennis voor zaken

ZonMw

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Quality indicators

- Quality indicator = measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality of care[1]
- Developed in a systematic consensus procedure, using written questionnaires[2,3]
- Clinical experts on RM care

$$\frac{\text{numerator}}{\text{denominator}} \text{ X 100 = ... \%}$$

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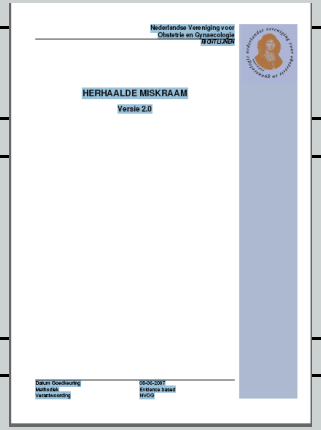
[1]Donabedian 1988, [2]Hermens 2006, [3]Mourad 2007

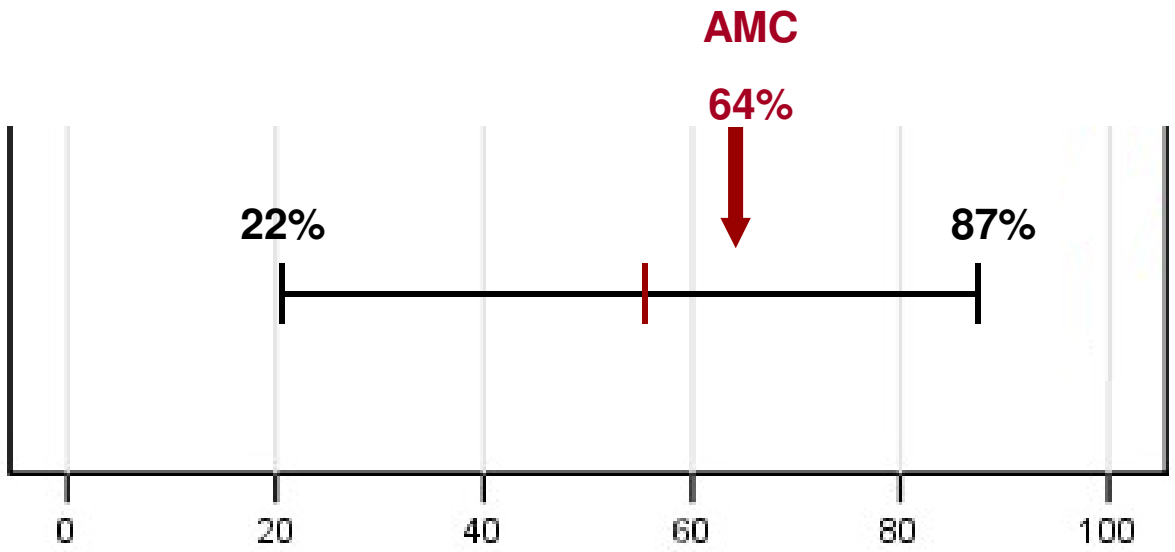
KEY RECOMMENDATIONS ELIGIBLE FOR INDICATOR TRANSCRIPTION		Level of evidence
1	Report the number of objectified miscarriages	D
Chromosome abnormalities		
2	Record maternal age at the time of the 2nd miscarriage	B
3	Ask for family history with regard to recurrent miscarriage in parents and brothers/sisters of both partners	B
4	Perform karyotyping selectively	B
5	Refer all couples which were found to be carrier of a balanced structural chromosome abnormality to a clinical geneticist	D
8	Start anticoagulant treatment in patients diagnosed with anti-phospholipid syndrome, according to the modified schedule of Rai	B
Trombophilia		
9	Report on history of thrombo-embolisms in all women	B
10	Report on family history of Thrombophilia and thrombo-embolisms	B
11	Perform screening for thrombophilia only in high risk patients	B
Homocystein		
12	Determine random homocystein in all patients	B
13	Supplement vitamins of low vitamin levels are found in hyperhomocysteinemia	C
Lifestyle		
14	Ask for lifestyle, including smoking habits of both patient and partner	B
15	Quit smoking for both patient and partner (in case of smoking)	B
16	Determine length and weight and calculate Body Mass Index (BMI)	B
17	Advise to loose weight,(in case of overweight)	B
General		
18	Prescribe new treatments *only* in the setting of a Randomised Clinical Trial	D
19	Withhold immunotherapy	A
20	Withhold therapy with aspirin in unexplained RM	B
21	Advise preconceptional folic acid (0,4-0,5 mg) to all patients	A
22	Offer Tender Loving Care in unexplained RM	C
23	Determine and discuss individual chances for success in the next pregnancy	B

1. Report the number of objectified miscarriages



van den Boogaard RBMonline in press

Report the no. of objectified miscarriages



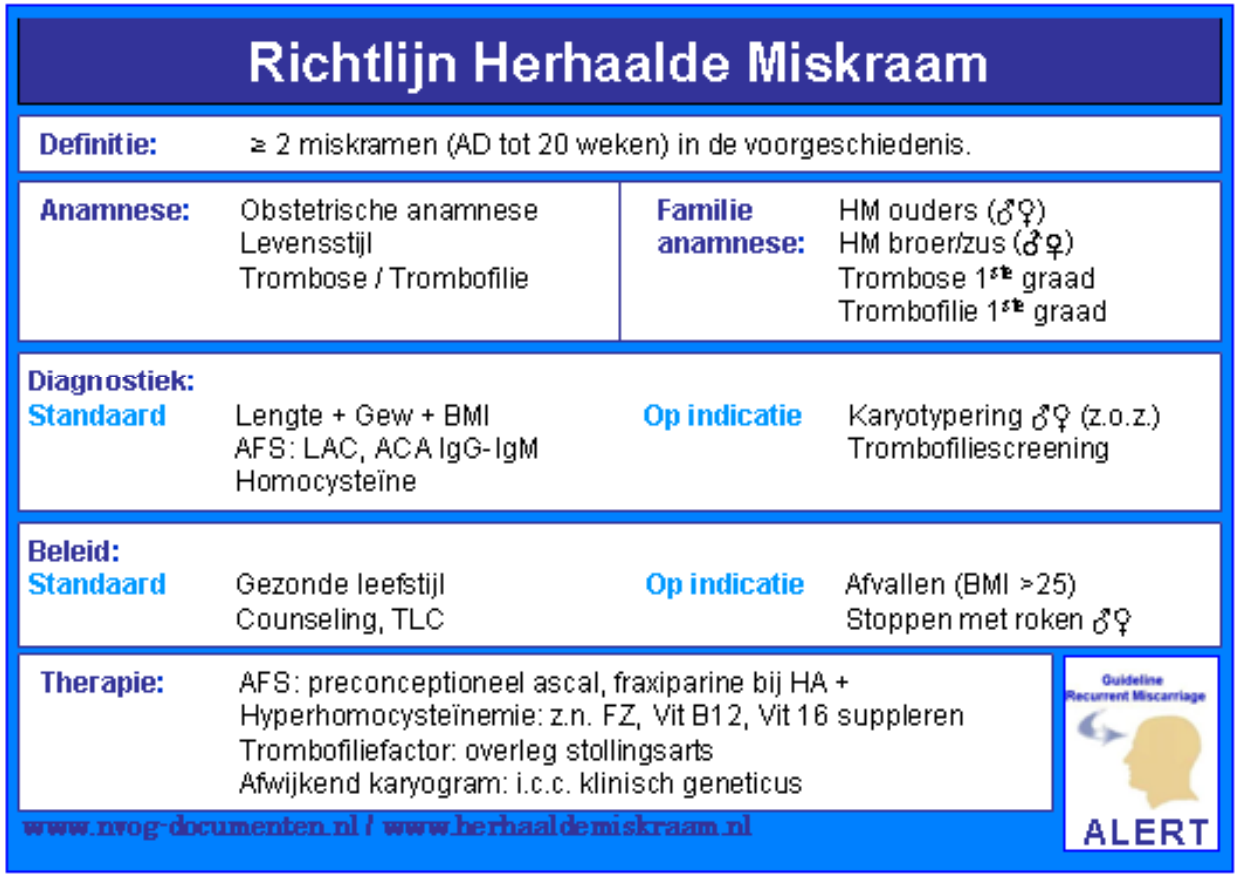
no of women with RM *and* documentation of no of obj misc

all women with RM

X 100 = … %

How to improve adherence?

Pocket card



Richtlijn Herhaalde Miskraam

Definitie: ≥ 2 miskramen (AD tot 20 weken) in de voorgeschiedenis.

Anamnese:
- Obstetrische anamnese
- Levensstijl
- Trombose / Trombofilie

Familie anamnese:
- HM ouders (♂♀)
- HM broer/zus (♂♀)
- Trombose 1ste graad
- Trombofilie 1ste graad

Diagnostiek:

Standaard
- Lengte + Gew + BMI
- AFS: LAC, ACA IgG-IgM
- Homocysteïne

Op indicatie
- Karyotypering ♂♀ (z.o.z.)
- Trombofiliescreening

Beleid:

Standaard
- Gezonde leefstijl
- Counseling, TLC

Op indicatie
- Afvallen (BMI >25)
- Stoppen met roken ♂♀

Therapie:
- AFS: preconceptioneel ascal, fraxiparine bij HA +
- Hyperhomocysteïnemie: z.n. FZ, Vit B12, Vit 16 suppleren
- Trombofiliefactor: overleg stollingsarts
- Afwijkend karyogram: i.c.c. klinisch geneticus

www.nvog-documenten.nl / www.herhaaldemiskraam.nl

Guideline Recurrent Miscarriage ALERT

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Electronic Decision aid

No of obj misc

Maternal age at 2nd misc

Length cm

Weight kg

Smoking (♀)

Passive smoking (♂)

Family History RM

–sibs

-parents

Thrombosis

Family history thrombosis

Family history Thrombophilia

www.freya.nl

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Electronic Decision aid

Advies programma bij herhaalde miskramen.

Relevante vragen	Antwoord	Advies
Rookt uw partner :	Ja	**Stoppen met roken.**
Lengte : Gewicht : BMI :	1.73 95 31.7	**Afvallen**
HM bij ouders van patiënte/partner : HM bij broer/zus van patiënte/partner : Aantal miskramen :	Nee Ja 5	**Risico op gebalanceerde chrom** **Karyotypering patiënte en partn**
Heeft u ooit trombose gehad : Trombose 1ste graads famililid : Trombofilie bij hetzelfde familielid :	Ja Nee Nee	**Trombofiliefactoren bepalen**
Standaard		**Antipfospholipiden antistoffen bepalen** **Homocysteïne bepalen** **Gezonde leefstijl** **Foliumzuur**

Naar uitslagen en beleid

Stop smoking

Loose weight

Risk of carrier status: 7.2%
=> parental karyotyping

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Definition evidence

- Absence of evidence
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- Try to define RM using data instead of discussions
  - 2 vs 3
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  - Gestational age of miscarriages

Does sequence matter?

Consecutive vs non-consecutive

- Case-control study (1: 2)
- Six centres for Clinical Genetics, The Netherlands[1,2]
- Period: 1992-2003
- Definition of consecutive: two preceding miscarriages in a row not interspersed with another pregnancy
- 707 couples
  - 279 carrier couples
  - 428 non-carrier couples

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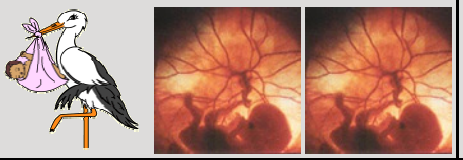
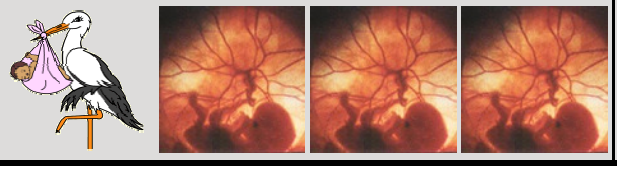
[1]Franssen BMJ 2005, [2]Franssen BMJ 2006

Consecutive vs non-consecutive

Examples of consecutive vs non-consecutive miscarriages

≥2 Consecutive miscarriages **LB-M-M / M- M** 	*≥2 Non-consecutive miscarriages* **M-LB-M** 
≥3 Consecutive miscarriages **LB-M-M-M / M-M-M** 	*≥3 Non-consecutive miscarriages* **M-M-LB-M-LB** 

M= miscarriage, LB=livebirth

Consecutive vs non-consecutive

Baseline characteristics for patients with ≥2 miscarriages

≥ 2 miscarriages (n=707)	**Carriers n=279**	**Non-carriers n=428**	**P-value**
Maternal age in years at time of chromosome analysis	31.8 (4.3)	32.7 (5.0)	0.012
Maternal age in years at second miscarriage	30.5 (4.2)	31.6 (4.9)	0.002
Number of preceding miscarriages before chromosome analysis	3.0 (1.2)	2.8 (1.1)	0.004
Number of preceding live births - median (min-max)	0.0 (0-6)	1.0 (0-5)	0.029
Consecutive miscarriages - number (%)	256 (92%)	381 (89%)	0.21

Consecutive vs non-consecutive

Baseline characteristics for patients with ≥3 miscarriages

≥ 3 miscarriages (n=386)	**Carriers n=170**	**Non-carriers n=216**	**P-value**
Maternal age in years at time of chromosome analysis	31.7 (4.3)	32.6 (5.3)	0.07
Maternal age in years at second miscarriage	29.9 (4.2)	30.8 (5.1)	0.06
Number of preceding miscarriages before chromosome analysis	3.7 (1.2)	3.5 (1.0)	0.20
Number of preceding live births - median (min-max)	1.0 (0-6)	1.0 (0-5)	0.14
Consecutive miscarriages - number (%)	132 (78%)	168 (78%)	0.98

Consecutive vs non-consecutive

Probability of carrying a structural chromosome abnormality

	Univariable regression analysis		Multivariable regression analysis*	
Covariates	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
≥2 consecutive miscarriages compared to ≥2 non-consecutive miscarriages	1.4 (0.83-2.39)	0.21	0.90 (0.48-1.7)	0.75
≥3 consecutive miscarriages compared to ≥3 non-consecutive miscarriages	0.99 (0.6-1.6)	0.98	0.71 (0.39-1.3)	0.25

* Corrected for known risk factors

Conclusions

- Testing in recurrent miscarriage should take place if it results in effective treatments or the determination of prognosis.
- Number of miscarriages, maternal age and family history are established riskfactors for carrier status and pregnancy outcome
- No evidence is available to take into account the sequence of preceding miscarriages.

Advice

- Refrain from fixed definitions in RM
- Use a broad definition: two preceding miscarriages
- After an accurate patient history, apply the available best evidence to determine whether to start testing in an individual patient or not

- Experimental diagnostics or treatment → RCT

Acknowledgment

Center for Reproductive Medicine:
Mariëtte Goddijn
Fulco van der Veen
Maureen Franssen

Department of Clinical Genetics:
Nico Leschot

Department of Clinical Epidemiology:
Patrick Bossuyt
Joke Korevaar

Radboud University Medical Center, Nijmegen
Rosella Hermens
Jan Kremer

Clinical Genetic Centers, The Netherlands:
A.C. Knegt (AMC)
K. Madan, A. Nieuwint (VUMC)
R. Hochstenbach (UMC Utrecht)
K.B.J. Gerssen-Schoorl, R.F.Suykerbuyk (UMC Groningen)
C.H. Wouters (Erasmus MC)
K.B.M. Hansson (LUMC)

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