

Anatomic factors and recurrent pregnancy loss

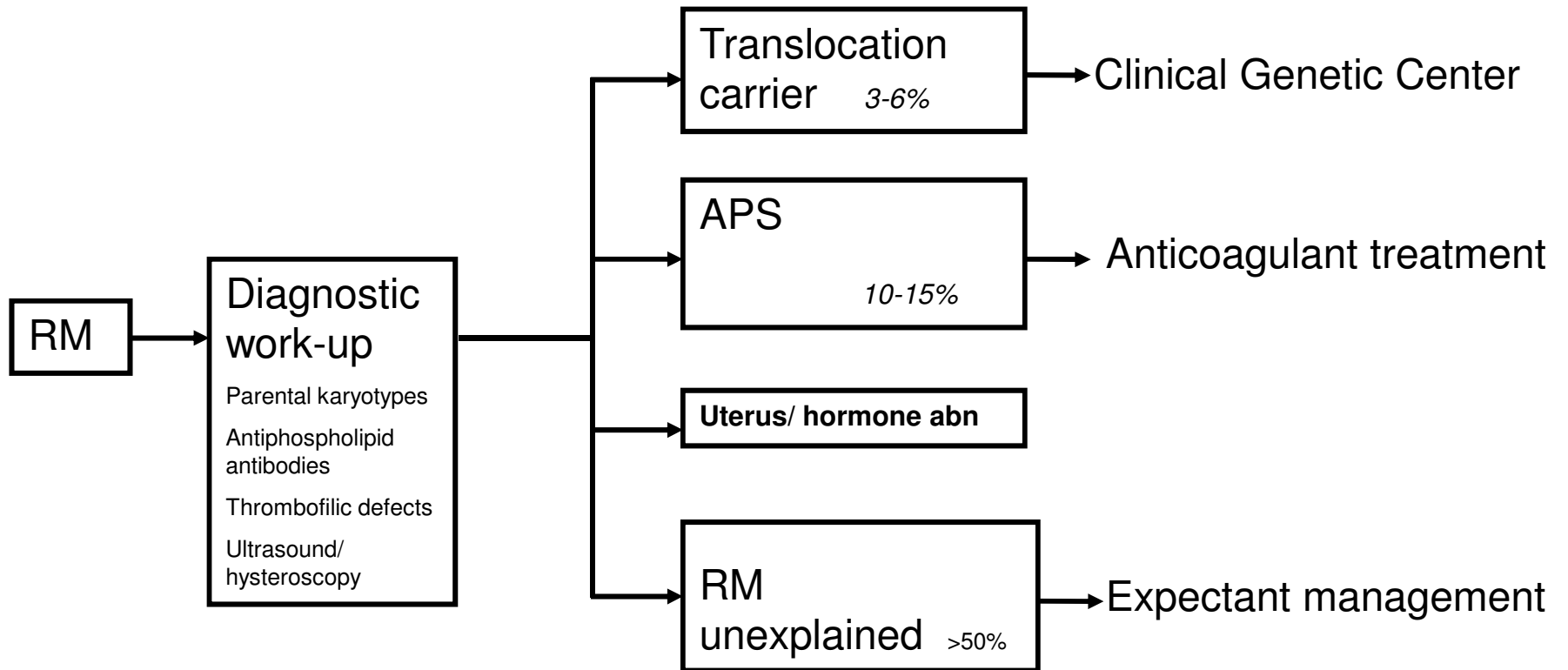
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Anatomic factors and recurrent pregnancy loss

- Background
 - Recurrent miscarriage work-up
 - congenital uterine anomalies
- Septate uterus and reproductive outcome
- Methodological pitfalls
- TRUST trial
- Conclusions

Recurrent miscarriage work-up



All couples: advise healthy life style

Recurrent miscarriage work-up

Advice¹

- favour evidence based management
- promote Randomised Controlled Trials

Practice²

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

¹Rai Lancet 2006, ²Franssen Hum Reprod 2007

Patient's view

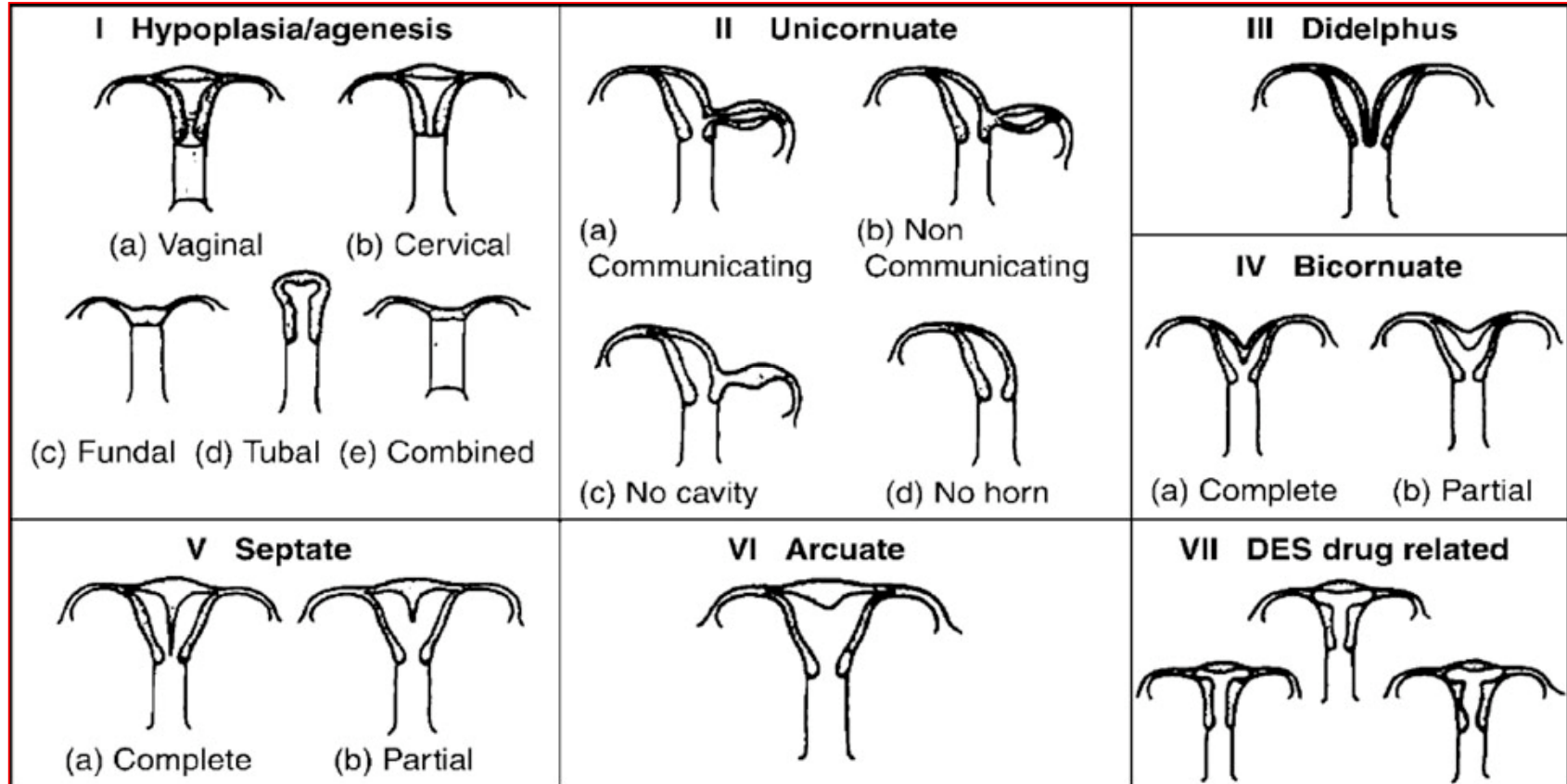


Background

- Frequency of most common congenital uterine anomalies:
 - Septate Uterus 35%
 - Bicornuate Uterus 25%
 - Arcuate Uterus 20%
- Prevalence of congenital uterine abnormalities in the:
 - General population ~ 4.3¹- 6.7²%
 - Subfertile population ~ 3.5¹- 7.3²%
 - Recurrent Miscarriage population ~ 13¹- 16.7²%
- Hysteroscopy and laparoscopy, SHG and 3D US are the most accurate diagnostic procedures²

¹Grimbizis HRU 2001, ²Saravelos HRU 2008

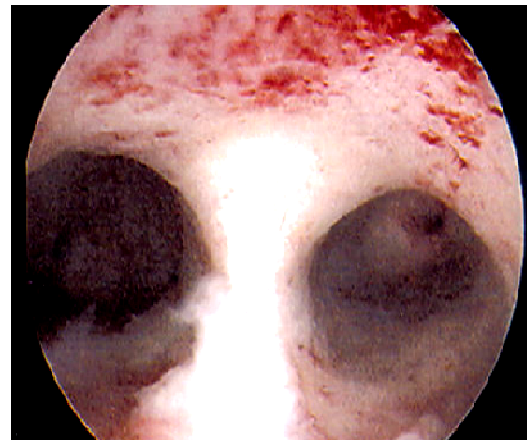
AFS Classification 1988



Classification problems: different diagnostic tools
criteria septate vs arcuate uterus

Septate Uterus

- Most common anomaly
- Higher incidence in couples with recurrent miscarriage
- Hysteroscopic resection is possible (metroplasty)
- Likely causal factor in poor reproductive outcome



Homer Fertil Steril 2000, Grimbizis HRU 2001, Lin Fertil Steril 2002
Saravolos HRU 2008

Biological plausible hypotheses

A septate uterus leads to poor reproductive outcome;

- Poor septum vascularization leading to poor decidualization and placentation^{1,2,3}
- Increased amount of muscle tissue in the septum can cause miscarriage by uncoordinated contractility
- Reduced length of unaffected uterine cavity
- Local defect of VEGF receptors⁴

¹Dabirashrafi 1995, ²Kupesic 1998 ³Kupesic 2001 ⁴Raga Fertil Steril 2009

Hysteroscopic metroplasty

- Commonly practiced
- Safe procedure
- Potential complications (0.95%)¹
 - Uterine perforation
 - Fluid overload
 - endometritis
- Unknown whether it is efficacious



¹Jansen FW Obstet Gynaecol 2000

Septate uterus and reprod outcome

TABLE 1

Outcome of pregnancies in women with complete septate uterus and longitudinal vaginal septum.

	Pregnancies	Spontaneous abortion ^a	Delivery		Live birth rate ^a
			Preterm ^a	Term ^a	
No metroplasty (n = 49) ^b					
First pregnancy	49	13 (27)	5 (10)	31 (63)	30 (61)
All pregnancies	115	31 ^c (27)	14 (12)	70 (61)	83 (72)
Metroplasty (n = 4)					
Before	8	7 ^d (87)	0	1 (13)	1 (13)
After	8	2 (25)	0	6 (75)	6 (75)

Uterine anomalies and reproductive outcome

TABLE 2

Successful reproductive outcome after examination of uterine anomalies in patients with recurrent miscarriage.

	Success rate per pregnancy					Cumulative success rate				
	With anomalies (n = 42)	Bicornuate	Septum	Without anomalies (n = 1528)	Difference in %	P	With anomalies (n = 41) ^a	Without anomalies (n = 1528)	Difference in %	P
Pregnancy after the ascertainment of uterine anomaly										
First	25/42 (59.5) ^b	21/37 (56.8)	4/5 (80.0)	1096/1528 (71.7)	-12.2	.084	25 (61.0)	1096 (71.7)	-10.7	.133
Second	5/9 (55.6)	4/8 (50.0)	2/2 (100)	166/275 (60.4) ^c	-4.8	.772	30 (73.2)	1262 (82.6)	-9.4	.119
Third	2/2 (100)	2/2 (100)		38/69 (55.0)	+45.0	.207	32 (78.0)	1300 (85.1)	-7.1	.215
Fourth				4/18 (22.2)				1304 (85.3)		
Fifth				3/9 (33.3)				1307 (85.5)		
Sixth				0/6 (0)				1307 (85.5)		
Final follow up							32 (78.0)	1307 (85.5)	-7.5	

Case-control study: No difference in cumulative live birth rate

Less aneuploid conceptions in the group with uterine anomalies (2/13 = 15.4%) compared to the group without uterine anomalies (134/233 = 58%)(P=.006)

Sugiura-Ogasawara Fertil Steril 2009

Results of intervention studies

TABLE 2

Comparison of reproductive outcome before and after hysteroscopic metroplasty for the septate uterus in selected series.

Author (ref.)	Before metroplasty					After metroplasty			
	No. of patients	No. of pregnancies	No. of miscarriages (%)	No. of preterm deliveries (%)	No. of term deliveries (%)	No. of pregnancies	No. of miscarriages (%)	No. of preterm deliveries (%)	No. of term deliveries (%)
Chervenak and Neuwirth (72)	2	3	3 (100)	0	0	2	0	0	2 (100)
Daly et al.* (70)	17	40	34 (85)	5 (12.5)	1 (2.5)	9	2 (22)	1 (11)	6 (67)
De Cherney and Polan* (81)	15	NR	>30	NR	NR	11	2 (18)	0	9 (82)
Israel and March* (71)	12	28	26 (93)	0	2 (7)	2	1 (50)	0	1 (50)
De Cherney et al. (79)	103	NR	>206	NR	NR	>71	>8	1	NR
Valle and Sciarra* (18)	12	42	30 (71)	12 (29)	0	10	2 (20)	2 (20)	6 (60)
Fayez (20)	12	21	19 (90)	2 (10)	0	16	2 (13)	0	14 (87.5)
March and Israel (16)	57	240	212 (88)	21 (9)	7 (3)	56	8 (14)	4 (7)	44 (79)
Perino et al. (33)	24	27	24 (89)	3 (11)	0	15	1 (7)	0	14 (93)
Daly et al. (69)	55	150	130 (87)	13 (9)	7 (5)	75	15 (20)	5 (7)	55 (73)
Choe and Baggish (17)	14	38	31 (82)	6 (16)	1 (3)	12	1 (8.3)	1 (8.3)	10 (83.3)
Fedele et al. (73)	71	>139	>139	NR	NR	65	10 (16)	10 (16)	45 (69.2)
Cararach et al. (74)	62	176	160 (91)	11 (6)	5 (3)	41	12 (29)	0	29 (48)
Pabuccu et al. (76)	49	108	96 (89)	11 (10)	1 (1)	44	2 (4.5)	2 (4.5)	40 (9.1)
Valle (77)	115	299	258 (86.3)	28 (9.4)	13 (4.3)	103	12 (12)	7 (7)	84 (81)
Mencaglia and Tantini† (40)	94	NR	>94	NR	NR	62	4 (6)	0	58 (94)
Total	658	1,062	933 (88)	95 (9)	34 (3)	491	67 (14)	29 (6)	395 (80)

Results of intervention studies

Before metroplasty			After metroplasty		
No. of miscarriages (%)	No. of preterm deliveries (%)	No. of term deliveries (%)	No. of miscarriages (%)	No. of preterm deliveries (%)	No. of term deliveries (%)
933 (88)	95 (9)	34 (3)	67 (14)	29 (6)	395 (80)
	12%			86%	

74% 'increase'

Homer Fertil Steril 2000

However

Surgeons report in another way
than non-surgeons

spontaneous pregnancy rate RM unexplained

Success rate
Number of miscarriages

	<i>N=222</i>	2	3	4	5
female age	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

'before-after' spontaneous conception

- Obstetric history in 325 unexplained RM cases:
 - 1052 preceding miscarriages
 - 152-195 preceding livebirths

=> success rate ~ 15 (13-16)%
 - Obstetric outcome in 226 unexplained RM cases:
 - 55 subsequent miscarriages
 - 167 subsequent livebirths

=> success rate ~ 75%
- => ~ 60% improvement of LBR by dedicated care only (exp management)!

before-after comparisons

- Not a fair comparison
- Poor obstetric history is the indication for an intervention
- Women with a septate uterus without RM are not included
- The outcome without intervention is likely to be improved by chance
- Comparing pregnancy outcome of an intervention vs non-intervention can only be done by RCT

Christiansen 2005, Twisk 2006

Barriers to perform a RCT

- Patients might insist on an intervention
- Logistical barriers
- Difficult to randomize sufficient number of patients
- Guidelines' recommendations (low level evidence)
- My patients pay their own treatment

RM Guidelines' recommendations

Perform hysteroscopic metroplasty or not?

ACOG 2001: women with pregnancy loss and a uterine septum should undergo hysteroscopic evaluation and resection (evidence level C)

RCOG 2003: no results of RCT's available

ESHRE 2006: (not addressed)

NVOG 2007: do not perform uterine surgery unless in the context of a clinical trial

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

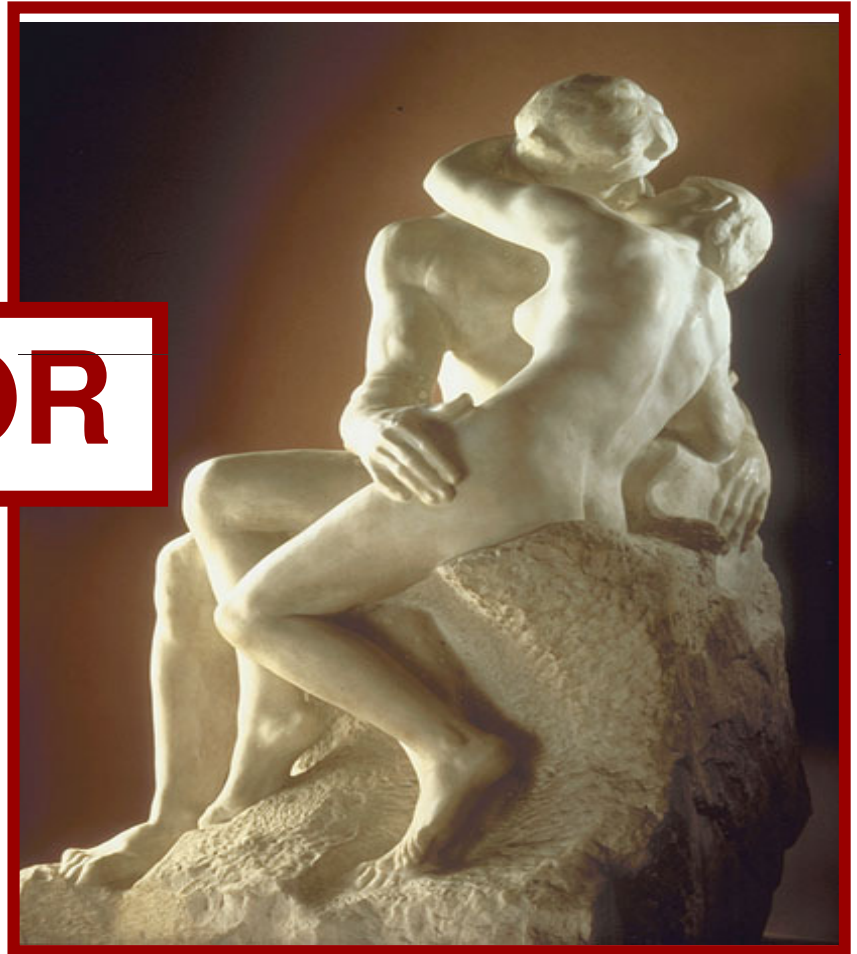
NVOG guideline Recurrent Miscarriage 2007
translation: NGC website www.guideline.gov

metroplasty?

spontaneous?



OR



- **T**he **R**andomised **U**terine **S**eptum **T**ranssection trial
- Does surgical correction of the septate uterus (hysteroscopic septoplasty) in women with RM improve live birth rate?
- Random allocation to hysteroscopic metroplasty or no intervention

- Inclusion criteria:
 - Recurrent miscarriage (≥ 2 miscarriages < 20 weeks)
 - Proven Uterus septus
 - Septum length minimal $\frac{1}{4}$ of cavity length measured at HSG
 - Active child wish

TRUST Outcome measures

- Primary outcome measure:
 - Live birth rate (>24 wks)
- Secondary outcome measures:
 - Complications of hysteroscopic septumtranssection
 - Pregnancy complications/ outcomes

Follow up includes first subsequent pregnancy (≤ 1 year)

Repeat HSG and hysteroscopy 6-8 weeks after surgical intervention

Multi centre (inter) national randomized controlled trial



AMC = non-surgical coordinating trial center

Conclusions

- Increased prevalence of congenital uterine anomalies in women with RM
- The effect of surgical correction (hysteroscopic metroplasty) on reproductive outcome is unknown
- ‘Before-after’ comparisons should be forbidden
- RCT’s are urgently needed
- Adopting the guideline advise ‘only perform surgery in the context of a clinical trial’ might be of help

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Sample size TRUST study

- Estimated “live birth rate” is 35% without and 70% with hysteroscopic septoplasty
- Alpha-error 5%, Beta-error 20%
- Two groups of 31 women needed to detect a difference
- 68 women need to be randomised



Bicornuate uterus

Brook 2002