



Recurrent Miscarriage

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Evidence Based Guidelines

- ★ Newly published for the investigation and medical treatment of recurrent loss
- ★ Updated version of ESHRE Special Interest Group in Early Pregnancy
- ★ Published Sept 2006 Human Reproduction v 21, no 9 p 2216-22
- ★ E. Jauniaux, RG Farquharson, OB Christiansen, N. Exalto

Methods

- ★ New large randomized controlled trials and meta analyses were used
- ★ Benefits have been reported for many endocrinologic and immunologic treatments, there is still controversy due to wide variations in patient selection criteria, treatment protocols, small sizes of individual studies, poor stratification bias and matching of cases and controls- limited translation of results into clinical practice.

ESHRE Guidelines

- ✦ Did not review surgical treatment of uterine causes of RM, nor the value of PGS for the embryos of couples presenting with RM

Introduction

- ★ RM affects around 1% of fertile couples
- ★ Defined as 3 or more miscarriages occurring before 20 weeks post menstruation
- ★ Risk of recurrence increases with maternal age and with number of successive losses
- ★ Prognosis is not better for couples with subsequent live birth (Clifford 1997)

Most Important

- ★ Number of previous miscarriages and maternal age are the most important co-variants
- ★ Have to take into account in planning therapeutic trials
- ★ Ideal trial should have stratification for # of miscarriages and maternal age with randomization between control and experimental treatments

RM

- ✱ Directly associated with parental chromosomal anomalies (Franssen et al 2005)
- ✱ Maternal thrombophilic disorders (Rey et al 2003)
- ✱ Structural uterine anomalies

RM

- ✦ Indirectly associated with
- ✦ Maternal immune dysfunction
- ✦ Endocrine abnormalities
- ✦ (Carrington et al 2005)

Idiopathic Group

- ★ **Majority** of RM cases- no identifiable cause in either partner
- ★ Considerable heterogeneity- unlikely one single pathological mechanism
- ★ Considerable debate about the cause and association
- ★ Current research directed at implantation, trophoblastic invasion and placentation as well as embryopathic factors(Quenby 2002)
- ★ Most women with RM probably have several risk factors for miscarriage

Coagulation Investigations

- ★ Acquired maternal thrombophilia is a well recognized cause of RM
- ★ All women with a history of 3 or more early losses(before 10 wks) or 1 or more unexplained deaths at greater than or equal to 10 weeks with structurally normal fetus, 1 or more premature births less than or equal to 34 wks with severe PIH or placental insufficiency should be offered testing

Exclude Antiphospholipid Syndrome (APS)

- ✦ Lupus anticoagulant (LAC)
- ✦ Anti cardiolipin antibodies (aCL) known collectively as anti phospholipid antibodies (APA)
- ✦ Wilson et al 1999

Inherited Thrombophilia

- ✦ Increased incidence of early and recurrent fetal loss has been suggested in women with inherited thrombophilia including Factor V Leiden deficiency, activated protein C resistance, Prothrombin G20210A and Protein S deficiency (Dawood et al 2003 Rey et al 2003)

Inherited Thrombophilia Debate

- ★ Other authors have found no association between maternal thrombophilia and pregnancy loss < 10 weeks gestation (Roque 2004)
- ★ Some studies reported a decreased risk of miscarriage in women with inherited thrombophilia (Carp 2002 ,van Dunne 2005)
- ★ One study reported multiple genetic thrombophilic mutations in either partner seem to increase the risk of miscarriage in a subsequent pregnancy (Jivraj 2006)

Thrombophilia

- ★ Conclude larger epidemiologic studies are clearly needed to justify testing couples with RM for inherited thrombophilias in routine clinical practice (Robertson 2006)

Other Coagulopathies

- ★ Other coagulation abnormalities including impaired fibrinolytic activity, Factor XII deficiency and reduced activated partial thromboplastin time have been reported to be associated with RM but corresponding epidemiological data are limited (Li 2002)
- ★ Assay for these abnormalities should only be performed as part of prospective clinical trials

Endocrinologic Investigations

- ✦ Early epidemiologic data show association between RM and hypothyroidism or diabetes mellitus
- ✦ Current evidence indicates that treated hypothyroidism and well controlled diabetes are not associated with RM (RCOG 1998)

Endocrine Investigations

- ★ Thyroid function tests and Hb A1C are accurate and inexpensive and can still be considered as part of the evaluation of RM (Christiansen 2005)
- ★ Low level of maternal thyroxine and poorly controlled diabetes in early pregnancy are associated with short and long-term consequences for fetal development and should be treated before conception

Obesity

- ★ Associated with a statistically increased risk of first trimester and recurrent miscarriage (OR 1.2 and 3.5 95% CI 1.01-1.46 and 1.03-12.01 respectively (Lashen 2004))

Obesity

- ★ Obesity has a wider impact on women's health – the association between PCO and RM could be secondary to the association between obesity and miscarriage (Fedorcsak 2000, Bellver 2003)
- ★ Weight loss should be first line therapy if overweight and infertile (Clarke 1998, Morikawa 2004) and there is little doubt the same should apply to RM

Other Endocrinologic Disorders

- ✦ Hypersecretion of LH, high androgen levels, hyperprolactinemia, and luteal phase defects have been associated with RM
- ✦ Current evidence suggests that, as with hypothyroidism, infertility is more of a problem than RM
- ✦ Further studies are required to examine the relationship between hyperandrogenism and RM (Christiansen 2005)

Immunologic Investigations

- ✦ Excessive maternal immune response against paternal antigens resulting in abnormal immune cells and cytokine production is still thought to be one of the causes of RM (Laird et al 2003)
- ✦ Still research on NK (natural killer) cells and RM relationship

Contradictory Evidence

- ✱ Suggest differences in the peripheral blood NK-cell levels in women with RM
- ✱ NK cells also found in endometrium and decidua but knowledge on their role in human placentation is limited
- ✱ Phenotypic and functional differences in NK cells from periphery or uterine, and peripheral tests give no useful information on uterine cells(Moffett 2004)

NK Cell Debate

- ✦ Percentage of CD 56+ NK cells in the periphery in healthy individuals varied from 5-29 % and is affected by sex, stress, ethnicity and age
- ✦ No routine measurement is recommended in RM or miscarriage in general (Rai 2005) outside research protocols

Peripheral Cytokines

- ✦ No scientific basis for measurement in peripheral blood in routine practice
- ✦ Recent research shows a high number of uterine NK cells in the endometrium of women with RM and could reduce with therapy (Quenby 2005) but need prospective trials before doing biopsies

Mannan-binding Lectin (MBL)

- ★ A C-type lectin that is part of the innate immune defence system activating complement on the surfaces of microorganisms
- ★ 2 large case controlled trials (Kilpatrick 21995 and Kruse 2002) showed low levels of MBL are associated with RM and low MBL is associated with a 20% higher(significant) miscarriage rate in the next pregnancy

MBL

- ★ Most women with low MBL levels do not experience RM
- ★ Suggests: that low MBL as a sole factor probably does not cause RM but may increase the risk of early pregnancy loss when found in conjunction with other immunological disturbances which remain to be investigated

Parental Cytogenetic Investigation

- ✦ Incidence of structural chromosomal abnormalities, usually a balanced translocation is increased in RM couples
- ✦ 4 factors: low maternal age at 2nd miscarriage, hx of 3 or more miscarriages, hx of 2 or more miscarriages in a brother or sister, and hx of 2 or more miscarriages in the parents of either partner increase the probability of carrier status (Franssen 2005)

Parental Cytogenetic Analysis

- ★ After 1 miscarriage it is generally accepted to refrain from karyotyping
- ★ The incidence of carrier status after 1 miscarriage is 2.2% (Braekeleer de and Dao 1990)
- ★ Refer for parental karyotype only when the probability of carrier status is greater than or equal to 2.2%

Probability of Carrier Status

Mat Age at 2nd loss		RM+ parent>/ =3 losses	2 losses	RM- Parent >/=3 losses	2 losses		
<23	+bs	10.2	7.3	7.3	5.2		
	-bs	5.7	4.0	4.1	2.8		
23-33	+bs	10.0	7.2 4.0	7.2	5.1		
	-bs	5.7		4.0	2.8		
34-36	+bs	5.8	4.1	4.1	2.9		
	-bs	3.2	2.2	2.2	1.6		
37-38	+bs	4.0	2.8	2.8	2.0		
	-bs	2.2	1.5	1.5	1.1		
>39	bs+	1.8	1.2	1.3	0.9		
	bs-	1.0	0.7	0.7	0.5		

Histopathology and Cytogenetics Investigations

- ★ Routine practice to send POC for histologic exam to exclude GTD- usefulness is debatable for future pregnancy management in RM
- ★ Inaccuracy of villous morphology and limited clinical significance of finding aneuploidy in sporadic miscarriage has led some to say it is valueless

Histopathology

- ★ In couples with RM there are a few reports of an increased incidence of thrombo-inflammatory lesions such as perivillous fibrin deposition, chronic villitis and deciduitis (Doss 1995, Hustin 1996) in particular when the karyotype is normal
- ★ These lesions support the immunologic imbalance concept, doesn't yet change management

Cytogenetics

- ★ Risk of live born trisomy after an aneuploidy in a sporadic early pregnancy failure is around 2%
- ★ In RM a normal karyotype in a previous loss is a predictor of subsequent loss
- ★ Women <36 with RM have a higher frequency of euploid loss
- ★ When stratified for maternal age, there is no difference in the distribution of cytogenetically abnormal miscarriages in RM compared with controls (Stephenson)

Cytogenetics

- ★ The cost benefit ratio of performing systematic karyotyping of POC after 1 miscarriage on the overall management of RM needs to be investigated prospectively in large populations

Anatomical Investigations

- ★ prevalence and impact on reproduction of uterine malformations in the general population is not clear
- ★ IN RM laparoscopy, HSG and /or hysteroscopy have been used to diagnose these malformations
- ★ US and particularly 3D US have become accurate, reproducible, noninvasive and outpatient methods for diagnosis (Salim 2003)

Anatomic Investigations

- ✦ Using 3D US it has been reported that women with a subseptate uterus have a higher incidence of first trimester loss, whereas women with an arcuate uterus have a greater proportion of second trimester loss and preterm delivery (Woelfer)

Anatomic Investigations

- ★ A large comparative study of the US morphology of congenital anomalies in women with and without RM has shown no difference in the relative frequency of various anomalies between the 2 groups of women
- ★ However with both arcuate and subseptate uteri the length of the remaining cavity was shorter and the size of the fundal distortion was higher in the RM group (Salim 2003)

Other Investigations

- ★ High level of homocysteine can be associated with RM
- ★ Among genetic causes polymorphism at position 677 in the MTHFR gene is a common one
- ★ Low plasma folate has been associated with an increased risk of first trimester loss (George 2002)- technically difficult investigation

Infections

- ✦ With bacteria, viruses or parasites can all interfere with early pregnancy development but none seems to be a significant cause of RM (Simpson 1996)
- ✦ Toxo, Rubella CMV and Herpes (TORCH) screen is therefore of limited value in RM outside an acute infectious episode

Toxins

- ✦ Association between miscarriage and ionizing radiation, organic solvents, alcohol, mercury, and lead is confirmed
- ✦ Association between caffeine, hyperthermia and cigarette smoking is suspected- Gardella and Hill(2000)

Recommended Testing in RM

- ★ Basic: Ob and family hx, age, BMI, organic solvents, alcohol, mercury, lead, caffeine, hyperthermia, smoking
- ★ Full blood count, TSH and blood sugar
- ★ LAC, aCL
- ★ Parental karyotypes
- ★ Pelvic US(SIS) or HSG/ hysteroscopy, laparoscopy

Recommended Testing in Trials

- ✱ Fetoplacental karyotypes
- ✱ Uterine or peripheral NK cells
- ✱ Mannan-binding lectin level
- ✱ Luteal phase Endometrial biopsy
- ✱ Homocysteine/folic acid level
- ✱ Thrombophilia screening

Recommended Medical Treatment in RM

- ★ TLC and health advice (diet, coffee, alcohol, smoking)
- ★ Need more RCTs
- ★ ASA and/or LMW heparins for APS or multiple inherited thrombophilias
- ★ P4 in women with unexplained early or late RM
- ★ IVIG in women with unexplained 2ary RM or late RM
- ★ Folic acid in hyperhomocysteinemia women
- ★ Immunization with third party donor leukocytes

Treatment of No Proven Benefit in RM

- ✱ Immunization with paternal leukocytes or trophoblast membranes
- ✱ Multivitamins supplementation
- ✱ Tx with more harm than benefit: daily corticosteroid in first half of pregnancy

Progesterone

- ★ Progesterone has been administered orally IM and intravaginally for more than 5 decades to attempt to prevent miscarriage in early to mid pregnancy
- ★ Overall the use is not associated with adverse affects in mothers
- ★ Carmichael recently reported maternal intake of progestins in early pregnancy is associated with an increased risk of hypospadias in male offspring (OR 3.7 95% CI 2.3-6)

Progesterone

- ✦ Despite considerable use, there is insufficient information to recommend optimal dose route timing of progesterone supplementation
- ✦ Recent systematic review found no evidence to support the routine use of progesterone in the first trimester to prevent miscarriage(Oates-Whitehead 2005)

Metaanalysis on Progesterone

- ✦ In a subgroup analysis of 3 trials, in RM, progesterone treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no treatment (OR 0.39 95% CI 0.17-0.91)
- ✦ Route of administration did not affect the results
- ✦ All trials were more than 40 years old

TLC

- ★ Small number of nonrandomized trials report psychological support in early pregnancy decreases miscarriage rate in unexplained miscarriage(Stray-Pederson)
- ★ Those with support and counselling had 86% pregnancy success compared to 33% in observed women with no specific AN care
- ★ Clifford found those attending early pregnancy clinic had 26% loss rate in subsequent pregnancy compared to 51% for those not attending

RCT

- ✱ TLC and health advice are the only interventions that do not require more RCTs
- ✱ All other proposed therapies which require more investigations are of no proven benefit or are associated with more harm than good.