PGT for RECURRENT

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› Hum Reprod. 2016 Aug;31(8):1668-74. doi: 10.1093/humrep/dew135. Epub 2016 Jun 7.

Intent to treat analysis of in vitro fertilization and preimplantation genetic screening versus expectant management in patients with recurrent pregnancy loss

Gayathree Murugappan [1], Lora K Shahine [2], Candice O Perfetto [3], Lee R Hickok [2], Ruth B Lathi [3]

The standard of care for management of patients with RPL is EM. Due to the prevalence of aneuploidy in CM, PGS has been proposed as an alternate strategy for reducing CM rates and improving LB rates.

Among all attempts at PGS or EM among RPL patients, clinical outcomes including pregnancy rate, live birth (LB) rate and clinical miscarriage (CM) rate were similar

Success rates with PGS are limited by the high incidence of cycles that intend but cancel PGS or cycles that do not reach transfer. Counseling RPL patients on their treatment options should include not only success rates with PGS per euploid embryo transferred, but also LB rate per initiated PGS cycle. Furthermore, patients who express an urgency to conceive should be counseled that PGS may not accelerate time to conception.

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rticle Contents

ferences

PGS for recurrent pregnancy loss: still an open question FREE

Laura Rienzi ✉, Antonio Capalbo, Gabor Vajta, Filippo Maria Ubaldi

Human Reproduction, Volume 32, Issue 2, 1 February 2017, Pages 476–477,
https://doi.org/10.1093/humrep/dew311
Published: 23 January 2017

human reproduction

LETTERS TO THE EDITOR

PGS for recurrent pregnancy loss: still an open question

Sir,

the risk of miscarriage. The misleading conclusion of the study was that expected management is the preferred option for patients with RPL, while a reliable comparison was not performed.

We suggest reconsideration of the approach described by the Authors in the clinical management of PGS cycles. Our points are the

- Available data prove that trophectoderm biopsy (Scott *et al*., 2013) and vitrification do not compromise the reproductive competence of blastocysts (Schoolcraft *et al*., 2011).

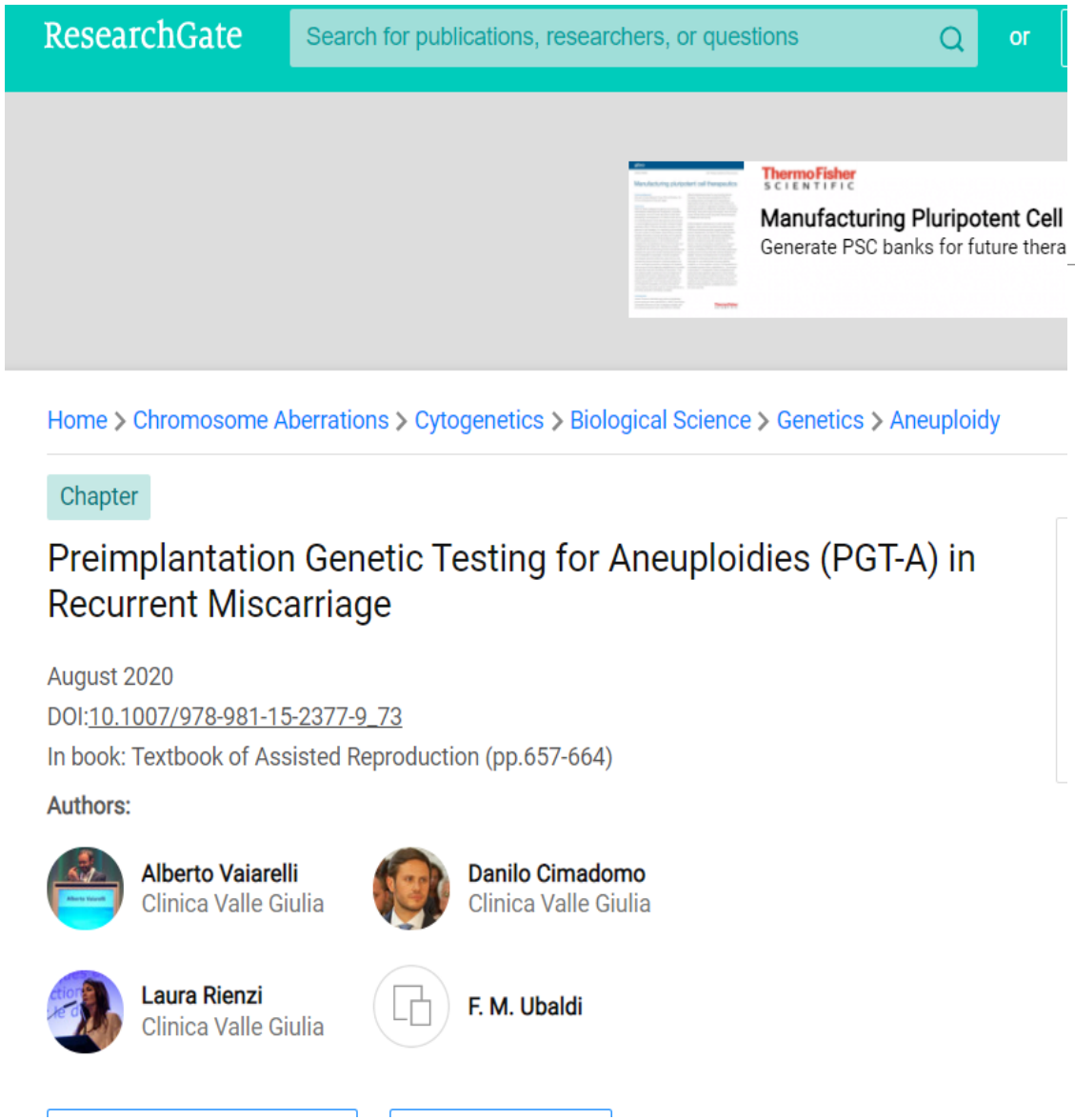
- –Morphological criteria, even coupled with morphokinetic analysis, are very poor predictors of embryo chromosomal architecture and viability (Capalbo *et al*., 2014; Rienzi *et al*., 2015).

- –Poor-quality blastocysts have significant euploidy rate and considerable delivery potential (Capalbo *et al*., 2014); poor embryo quality should not be used as a reason to cancel the genetic-testing procedure when PGS has been indicated before starting the IVF cycle.

- –PGS is not an indicative marker for embryo quality, but a definite genetic diagnostic test to exclude developmentally incompetent embryos from the cohort, those that are at risk to generate miscarriage or implantation failures.

Performing PGS in the cohort with poor embryo yield or quality—provided at least one embryo is available for biopsy—may help to eliminate frustrating failures and reduce the risks of miscarriages when chromosome testing is indicated for the couple (Chen *et al*., 2015). Establishment of criteria for the use of PGS in various embryo yield and quality situation will also help to obtain comparable results between IVF clinics.

In conclusion, we believe that the study performed by Murugappan and colleagues does not constitute a high quality of evidence to suggest forgetting the use of PGS in RPL patients



Recurrent miscarriage (RM) is an important issue in the field of reproductive medicine. It has been estimated that it affects 2–5% of the women trying to conceive. From a clinical perspective, few cases of RM are caused by a single cause; most of them may in fact have a multifactorial background which involves the interaction of multiple genetic and environmental parameters. Indeed, if the fertility rate decreases as the woman ages, the miscarriage rate follows an opposite trend. RM is one of the suggested indications to preimplantation genetic testing for aneuploidies (PGT-A). PGT-A is a comprehensive chromosome testing approach aimed at identifying chromosomally normal embryos within a cohort of blastocysts produced by a couple during an IVF treatment. This embryo selection strategy prevents aneuploid blastocysts from being transferred, thus reducing both the risk for implantation failure per transfer and miscarriage due to chromosomal impairments. However, some limitations to PGT exist, data about its clinical efficacy per intention to treat and cost-effectiveness are yet missing, and a clear international consensus has not been reached yet

Volume 2020, Issue 3
2020

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ESHRE PGT Consortium good practice recommendations for the organisation of PGT†

ESHRE PGT Consortium Steering Committee, Filipa Carvalho, Edith Coonen, Veerle Goossens, Georgia Kokkali, Carmen Rubio, Madelon Meijer-Hoogeveen, Céline Moutou, Nathalie Vermeulen, Martine De Rycke ✉

Human Reproduction Open, Volume 2020, Issue 3, 2020, hoaa021,
https://doi.org/10.1093/hropen/hoaa021

Published: 29 May 2020 **Article history** ▾

Abstract

PGT-SR: inclusion/exclusion

PGT-SR is an accepted and routine procedure in most IVF/PGT centers. It has been developed for patients who are unable to achieve a pregnancy or at high risk of pregnancy loss and of abnormal live born births, resulting from inheritance of unbalanced products of the rearrangement

PGT-A: inclusion/exclusion

Although PGT-A remains heavily debated in clinical practice, the following indications for its use have been reported:

•−AMA;

•−RIF;

•***−RM. It should be noted that couples with a history of RM have a high chance of successfully conceiving naturally and that PGT-A for RM without a genetic cause is not recommended in a recent evidence-based guideline (The ESHRE Guideline Group on RPL et al., 2018)***

•−SMF

RBMO

ELSEVIER

REVIEW

Clinical practice guidelines for recurrent miscarriage in high-income countries: a systematic review

BIOGRAPHY

Professor Keelin O'Donoghue is Consultant Obstetrician and Senior Lecturer at Cork University Maternity Hospital and University College Cork. She leads the multi-disciplinary Pregnancy Loss Research Group, has published over 154 peer-reviewed original papers and is Implementation Lead for the National Standards for Bereavement Care following Pregnancy Loss and Perinatal Death in Ireland.

Marita Hennessy[1,2,3,*], Rebecca Dennehy[1,2,3], Sarah Meaney[1,2,3,4], Laura Linehan[1,2,3], Declan Devane[2,5,6], Rachel Rice[1,7], Keelin O'Donoghue[1,2,3]

KEY MESSAGE

Thirty-two clinical practice guidelines (CPG) for recurrent miscarriage were identified. Levels of consensus across the CPG varied, with some conflicting recommendations. Greater efforts are required to improve the quality of evidence underpinning CPG, the rigour of their development and the inclusion of multi-disciplinary perspectives, including those with lived experience of recurrent miscarriage.

- **Eleven recommendations from six CPG related to 'genetic factors'**

  Two CPG stated that PGT should not be undertaken routinely (Practice Committee of the ASRM, 2012; Toth et al., 2018).

  One CPG stated that the value of PGT for aneuploidy (PGT-A) as a universal screening test for all IVF patients has yet to be determined (Practice Committees of the ASRM and the Society for Assisted Reproductive Technology, 2018).

  ESHRE PGT Consortium Steering Committee et al. (2020) recommended against PGT-A for recurrent miscarriage without a genetic cause.

  The RCOG (2011) and Practice Committee of the ASRM (2012) also made a point of declaring that PGT and IVF do not lead to a higher live birth rate in women who experience recurrent miscarriage, whereas the RCOG (2011) and ESHRE Early Pregnancy Guideline Development Group (2017) clearly stated the **natural live birth rate in this cohort is,** in fact, **higher than with PGT and IVF.**

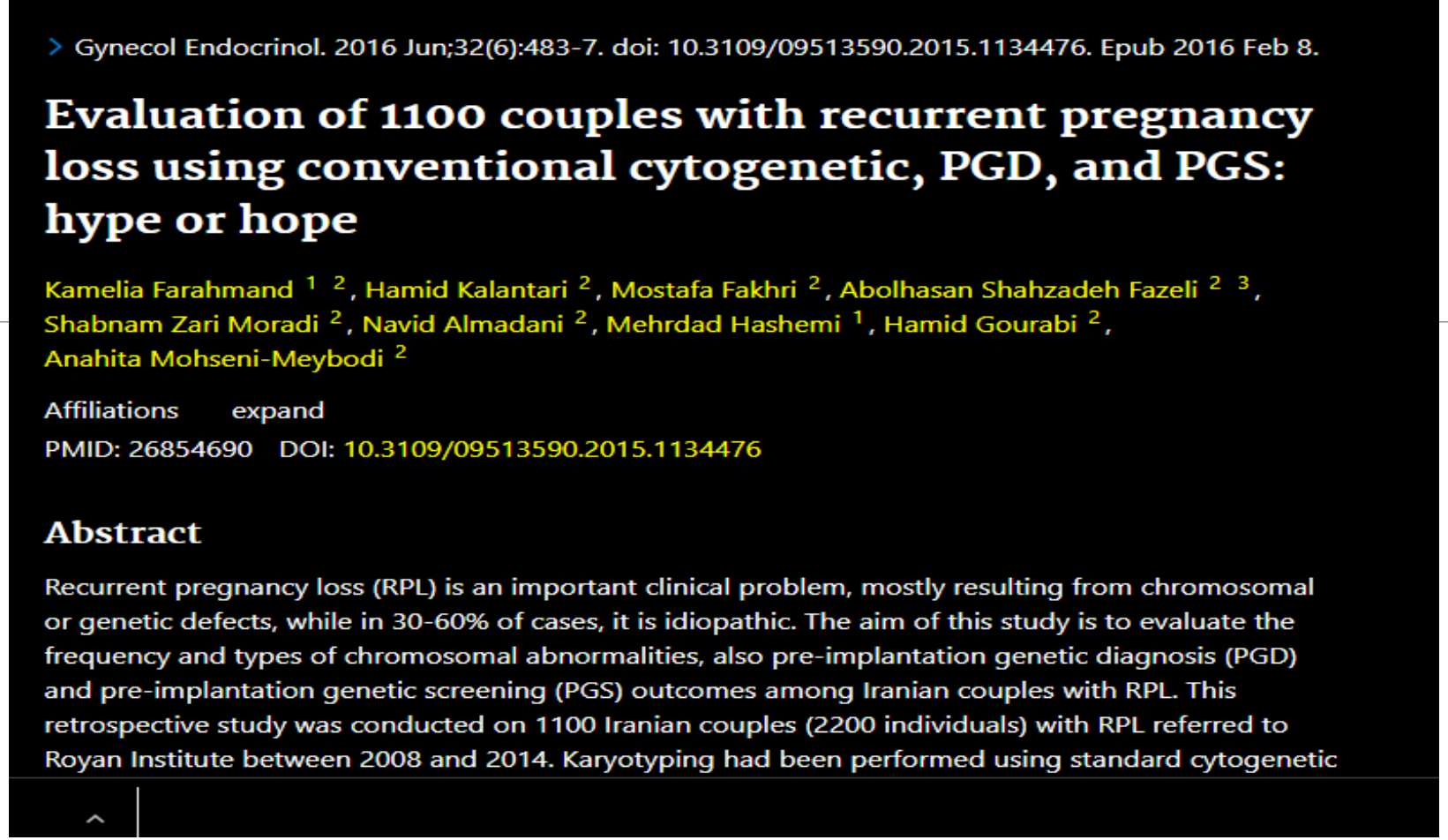
Comparative Study > Hum Reprod. 2019 Dec 1;34(12):2340-2348. doi: 10.1093/humrep/dez229.

Preimplantation genetic testing for aneuploidy: a comparison of live birth rates in patients with recurrent pregnancy loss due to embryonic aneuploidy or recurrent implantation failure

Takeshi Sato [1], Mayumi Sugiura-Ogasawara [1], Fumiko Ozawa [1], Toshiyuki Yamamoto [2],

Study design, size, duration: A multi-centre, prospective pilot study was conducted from January 2017 to June 2018. A total of 171 patients were recruited for the study: an RPL group, including 41 and 38 patients treated respectively with and without PGT-A, and an RIF group, including 42 and 50 patients treated respectively with and without PGT-A. At least 10 women in each age group (35-36, 37-38, 39-40 or 41-42 years) were selected for PGT-A groups.

Main result and the role of chance: There were no significant differences in the live birth rates per patient given or not given PGT-A: 26.8 versus 21.1% in the RPL group and 35.7 versus 26.0% in the RIF group, respectively. There were also no differences in the miscarriage rates per clinical pregnancies given or not given PGT-A: 14.3 versus 20.0% in the RPL group and 11.8 versus 0% in the RIF group, respectively. However, PGT-A improved the live birth rate per embryo transfer procedure in both the RPL (52.4 vs 21.6%, adjusted OR 3.89; 95% CI 1.16-13.1) and RIF groups (62.5 vs 31.7%, adjusted OR 3.75; 95% CI 1.28-10.95). Additionally, PGT-A was shown to reduce biochemical pregnancy loss per biochemical pregnancy: 12.5 and 45.0%, adjusted OR 0.14; 95% CI 0.02-0.85 in the RPL group and 10.5 and 40.9%, adjusted OR 0.17; 95% CI 0.03-0.92 in the RIF group. There was no difference in the distribution of genetic abnormalities between RPL and RIF patients, although double trisomy tended to be more frequent in RPL patients.



Gynecol Endocrinol. 2016 Jun;32(6):483-7. doi: 10.3109/09513590.2015.1134476. Epub 2016 Feb 8.

Evaluation of 1100 couples with recurrent pregnancy loss using conventional cytogenetic, PGD, and PGS: hype or hope

Kamelia Farahmand [1 2], Hamid Kalantari [2], Mostafa Fakhri [2], Abolhasan Shahzadeh Fazeli [2 3], Shabnam Zari Moradi [2], Navid Almadani [2], Mehrdad Hashemi [1], Hamid Gourabi [2], Anahita Mohseni-Meybodi [2]

Affiliations expand

PMID: 26854690 DOI: 10.3109/09513590.2015.1134476

Abstract

Recurrent pregnancy loss (RPL) is an important clinical problem, mostly resulting from chromosomal or genetic defects, while in 30-60% of cases, it is idiopathic. The aim of this study is to evaluate the frequency and types of chromosomal abnormalities, also pre-implantation genetic diagnosis (PGD) and pre-implantation genetic screening (PGS) outcomes among Iranian couples with RPL. This retrospective study was conducted on 1100 Iranian couples (2200 individuals) with RPL referred to Royan Institute between 2008 and 2014. Karyotyping had been performed using standard cytogenetic

The frequency of chromosomal abnormalities in these patients was 4.95%. Women demonstrated more abnormalities (6.82%) in comparison to men (3.09%). The successful rate of pregnancy after PGD and PGS was 52 and 18.64%, respectively

Current Opinion in
Obstetrics and Gynecology

REPRODUCTIVE ENDOCRINOLOGY: EDITED BY RUBEN ALVERO

A new algorithm for the evaluation of recurrent pregnancy loss redefining unexplained miscarriage: review of current guidelines

Papas, Ralph S.[a]; Kutteh, William H.[b,c]

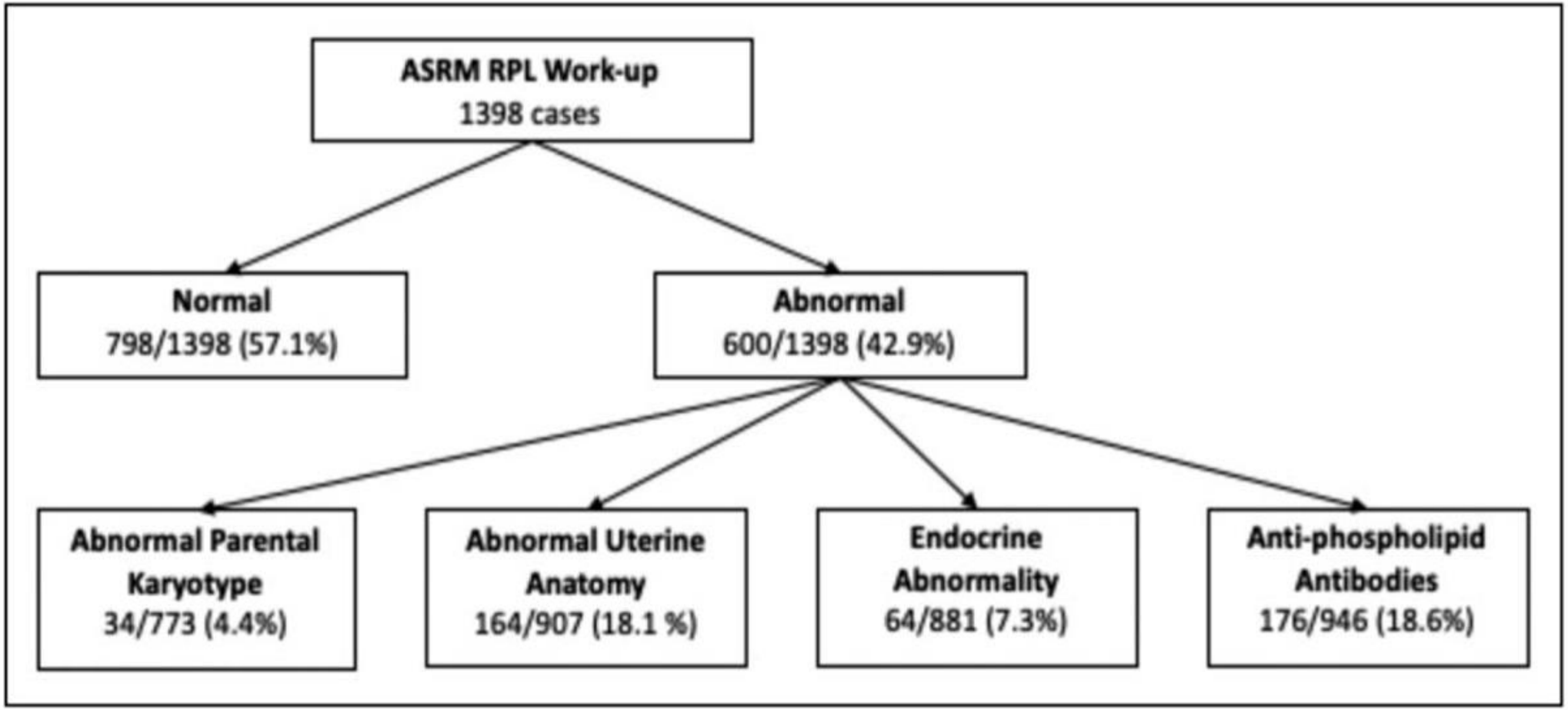
Author Information

Current Opinion in Obstetrics and Gynecology: October 2020 - Volume 32 - Issue 5 - p 371-379
doi: 10.1097/GCO.0000000000000647

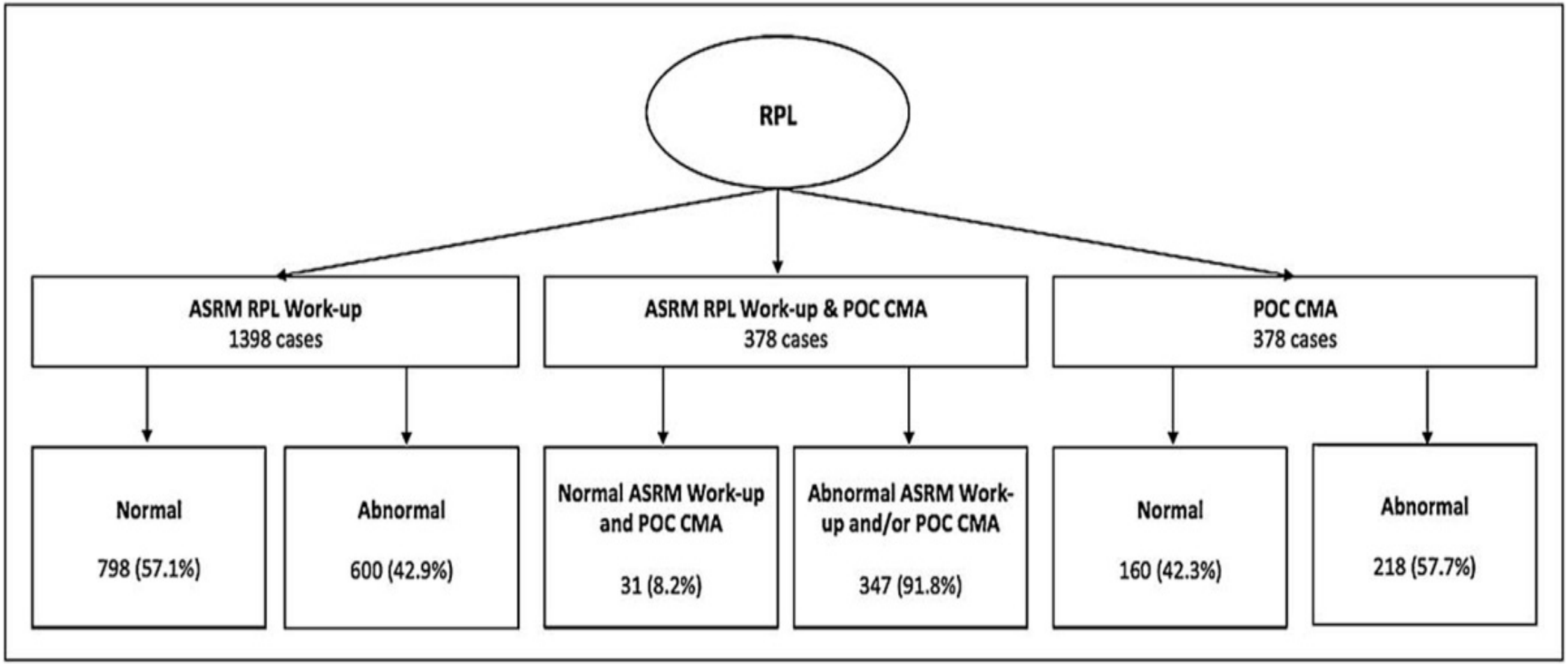
Screening test	Royal College 2011	ASRM 2012	ESHRE 2017	PROPOSED 2020
Parental karyotyping	Not recommended Unless POC reveals unbalanced translocation	Recommended	Conditional recommendation: Only after 'individual risk assessment'[a]	Not Recommended Unless POC CMA reveals unbalanced translocation
POC cytogenetic analysis	Recommended (after third and subsequent miscarriage)	Not recommended (karyotype analysis of POC only in the setting of ongoing therapy for RPL)	Conditional recommendation: for explanatory purposes (strong recommendation to use CMA when POC genetic analysis is performed)	Recommend: Use CMA for the second and subsequent pregnancy loss
Uterine anatomy evaluation	Recommended: If Pelvic ultrasound abnormal get Hysteroscopy or 3D ultrasound	Recommended: 3D ultrasound Hystero-salpingogram Hysteroscopy	Strong recommendation: (conditional recommendation: prefer 3D ultrasound)	Recommend: 3D ultrasound
Antiphospholipid antibodies	Recommended: lupus anticoagulant and anticardiolipin antibodies	Recommended: lupus anticoagulant Anticardiolipin antibodies Antiβ2 glycoprotein I	Strong recommendation: lupus anticoagulant and anticardiolipin antibodies Good clinical practice: antiβ2 glycoprotein I	Recommend: lupus anticoagulant, anticardiolipin antibodies, antiphosphtidyl serine antibodies
Thyroid function	Recommended: TSH	Recommended: TSH Not recommended: TPO	Strong recommendation: TSH and TPO antibodies	Recommend: TSH TPO when TSH > 2.5 mIU/l
Prolactin	Not discussed	Recommended	Conditional	Recommended

CMA VERSUS G-banding karyotype analysis FOR EVALUATION OF POC

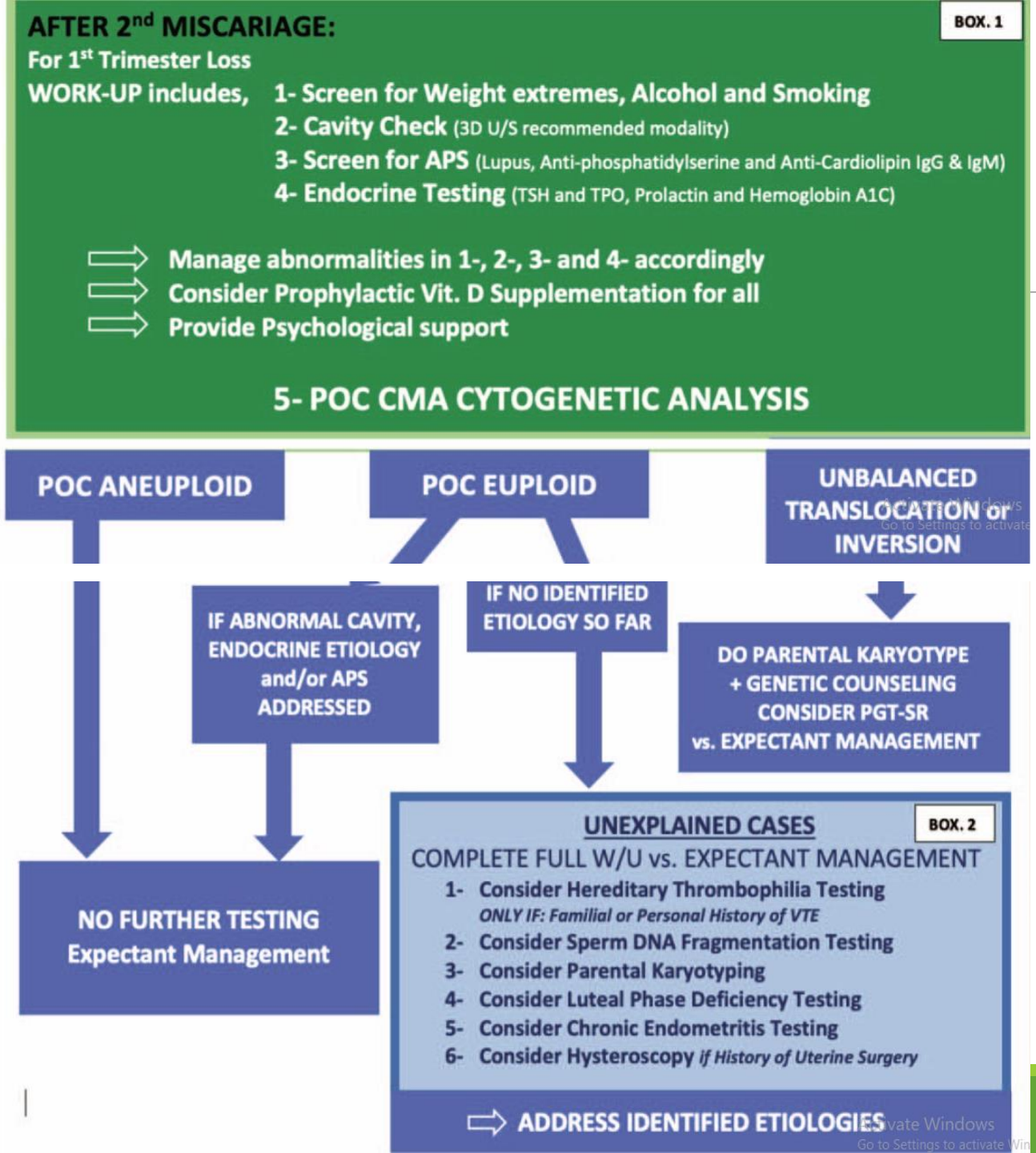
- The ASRM and RCOG positions on POC genetic testing for RPL were based on the then current standard of conventional G-banding karyotype analysis .
- ESHRE recommends CMA as the preferred modality for POC genetic testing because it is not limited by tissue culture failure or false negative results secondary to maternal cell contamination .
- Up to 50% of '46, XX normal' reports from POC testing result from maternal cell contamination, so methods to ensure the correct results are required .
- A recent report on CMA of 26 101 miscarriages had a successful read in over 86% of samples, detected 59% with a chromosomal anomaly that could explain a pregnancy loss, but reported 13% of total results were due to maternal cell contamination.
- Conventional cytogenetic results of 5457 consecutive POC samples yielded only 75% culture successes.
- Limitations of CMA technology include the inability to detect balanced structural chromosomal rearrangements and low-level mosaicism.



Results of the American Society for Reproductive Medicine Evaluation couples with recurrent pregnancy loss. A total of 1398 couples with two or more documented early pregnancy losses of 1398 had a complete evaluation as recommended by American Society for Reproductive Medicine [3]. More that 55% of couples had a normal evaluation and were classified as unexplained recurrent pregnancy loss. Updated from [5].



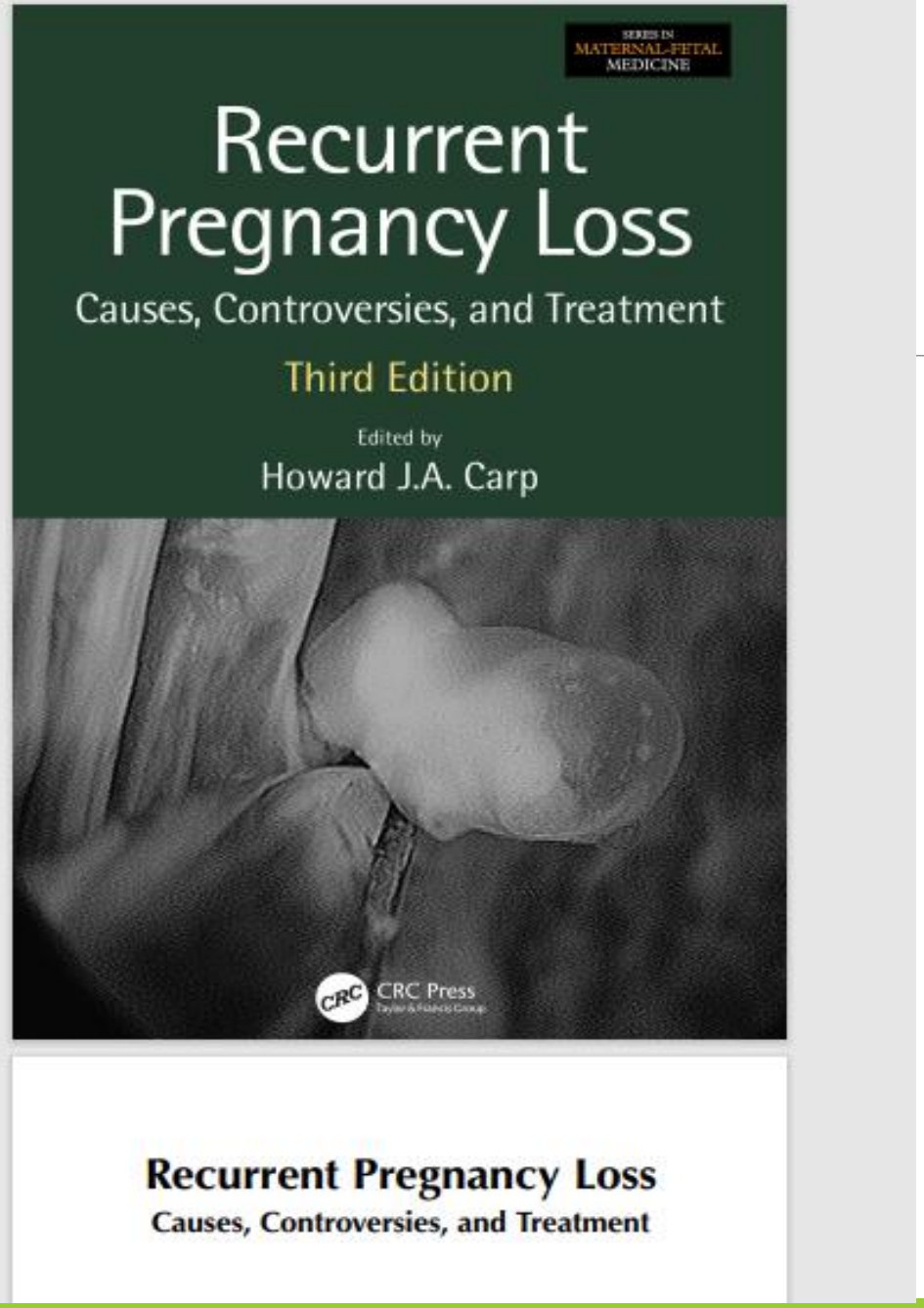
Three strategies for identifying the cause of recurrent pregnancy loss including American Society for Reproductive Medicine 2012 evaluation (left panel), products of conception chromosome microarray (right panel), and a combination of both (center panel). As shown on the left, only 42.9% of patients who were evaluated for recurrent pregnancy loss using the American Society for Reproductive Medicine recommendations had an explanation for their loss. When using only chromosomal microarray on products of conception as shown on the right, 57.7% of pregnancy losses were aneuploid and the couples had an explanation for their loss. When using the new strategy proposed in this article of combining chromosomal microarray on products of conception after the second or subsequent loss with a modified American Society for Reproductive Medicine evaluation (deleting parental chromosome analysis), 91.8% of couples had a possible or proven explanation for their loss (center panel).


AFTER 2nd MISCARIAGE:
BOX. 1
For 1st Trimester Loss
WORK-UP includes,
1- Screen for Weight extremes, Alcohol and Smoking
2- Cavity Check (3D U/S recommended modality)
3- Screen for APS (Lupus, Anti-phosphatidylserine and Anti-Cardiolipin IgG & IgM)
4- Endocrine Testing (TSH and TPO, Prolactin and Hemoglobin A1C)
Manage abnormalities in 1-, 2-, 3- and 4- accordingly
Consider Prophylactic Vit. D Supplementation for all
Provide Psychological support
5- POC CMA CYTOGENETIC ANALYSIS
POC ANEUPLOID
POC EUPLOID
UNBALANCED TRANSLOCATION or INVERSION
IF ABNORMAL CAVITY, ENDOCRINE ETIOLOGY and/or APS ADDRESSED
IF NO IDENTIFIED ETIOLOGY SO FAR
DO PARENTAL KARYOTYPE + GENETIC COUNSELING CONSIDER PGT-SR vs. EXPECTANT MANAGEMENT
NO FURTHER TESTING Expectant Management
UNEXPLAINED CASES
BOX. 2
COMPLETE FULL W/U vs. EXPECTANT MANAGEMENT
1- Consider Hereditary Thrombophilia Testing
ONLY IF: Familial or Personal History of VTE
2- Consider Sperm DNA Fragmentation Testing
3- Consider Parental Karyotyping
4- Consider Luteal Phase Deficiency Testing
5- Consider Chronic Endometritis Testing
6- Consider Hysteroscopy if History of Uterine Surgery
ADDRESS IDENTIFIED ETIOLOGIES

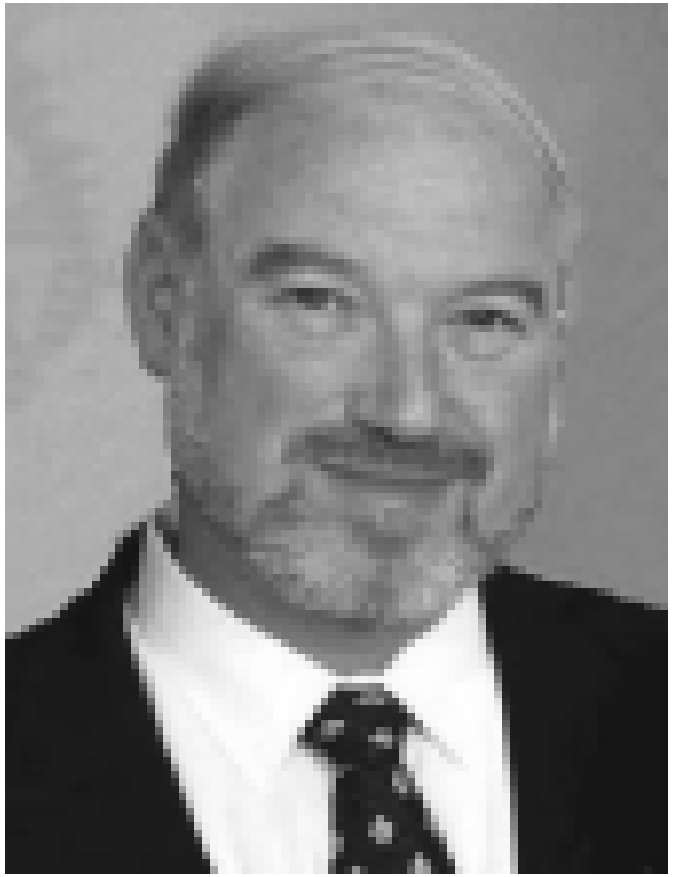
AFTER 3rd MISCARRIAGE:

BOX. 3

- If no testing has been done so far: Investigate and Manage according to above algorithm
- If above algorithm has been followed in previous miscarriage: Repeat POC Chromosomal Testing and Complete the full W/U if not already done
- If all possible known etiologies have been addressed and POC aneuploidy is repetitive, consider Expectant management vs. PGT-A


SERIES IN
MATERNAL-FETAL
MEDICINE
Recurrent
Pregnancy Loss
Causes, Controversies, and Treatment
Third Edition
Edited by
Howard J.A. Carp
CRC
CRC Press

Recurrent Pregnancy Loss
Causes, Controversies, and Treatment



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Empirical In Vitro *Fertilization for Recurrent Pregnancy Loss: Is It a Valid Concept?*

Michal Kirshenbaum and Raoul Orvieto

Conclusions

Although subfertility is not a problem in most couples with RPL, ART is often advised in RPL couples. However, scientific evidence is lacking. Patients might be interested in IVF in order to shorten time to conceive, but to date, IVF has not shown any benefit regarding the time to conceive.

Embryo quality has a significant role in the success of an ART cycle. ART includes methods to improve gametes and embryo quality, such as sperm selection, PGT-A, and morphologic examination. Although maximizing embryonal quality might improve the pregnancy outcome in couples with RPL, further adequately powered studies are needed to assess the results.

An abnormal endometrial microenvironment and changes in the functional expression of endometrial genes and protein might contribute to an abnormal embryonal-maternal interaction, resulting in pregnancy failure. Endometrial sampling for assessing endometrial receptivity and accurately timed embryonal transfer might improve this embryonal-maternal interaction. Nonetheless, due to the lack of studies investigating these methods in RPL patients, IVF cannot be recommended for this purpose.

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Debate: Should PGT-A Still Be Performed in Recurrent Pregnancy Loss? Yes

Carmen M. García-Pascual, Pilar López, Nasser Al-Asmar, Pere Mir, Lorena Rodrigo, Carlos Simon, and Carmen Rubio

Incidence of Aneuploidy in Products of Conception

Pregnancy loss is a common occurrence in humans, which may be attributable to several factors,

Conclusions

The chromosomal analysis of embryos before transfer in couples with either idiopathic RPL or RPL due to previous aneuploid embryos should be considered in order to improve pregnancy rates and live birth rates per pregnancy, and decrease the number of miscarriages, particularly if the miscarriages result from IVF.

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Debate: Should PGT-A Still Be Performed in Recurrent Pregnancy Loss? No

Raoul Orvieto and Norbert Gleicher

Introduction

A large majority of early pregnancy losses are the consequence of chromosomal abnormalities of the conceptus. If performed correctly, genetic analysis of products of conception therefore offers important

Conclusions

Although in most couples with RPL subfertility is not a problem, ART with PGT-A is often advised despite the absence of any supportive evidence. Patients might be interested in PGT-A to shorten the time to conceive, improve reproductive outcome, and reduce the miscarriage rate, but to date PGT-A has not shown any benefit in any of these parameters. Properly randomized controlled trials, which evaluate the cumulative live birth rates following a single oocyte retrieval, utilizing all fresh and frozen embryos in couples with unexplained RPL and no known chromosomal abnormality may be helpful in further clarifying the potential benefits of PGT-A. However, it appears increasingly obvious that the basic biology of the preimplantation human embryo simply does not support the PGS-hypothesis. It is therefore becoming increasingly difficult to expect any benefit from PGT-A.

1. Opinions are divided as to whether parental chromosomal aberrations should be examined. Testing is not recommended by ESHRE or the RCOG. However, if the fetus does inherit the chromosomal aberration in an unbalanced form, preimplantation genetic diagnosis may be appropriate treatment.
2. When fetal karyotypic aberrations are present, there is usually a good prognosis. However, there are patients with repeat aneuploidy (see Figure 19.3). PGT-A may be appropriate in cases of repeat aneuploidy.

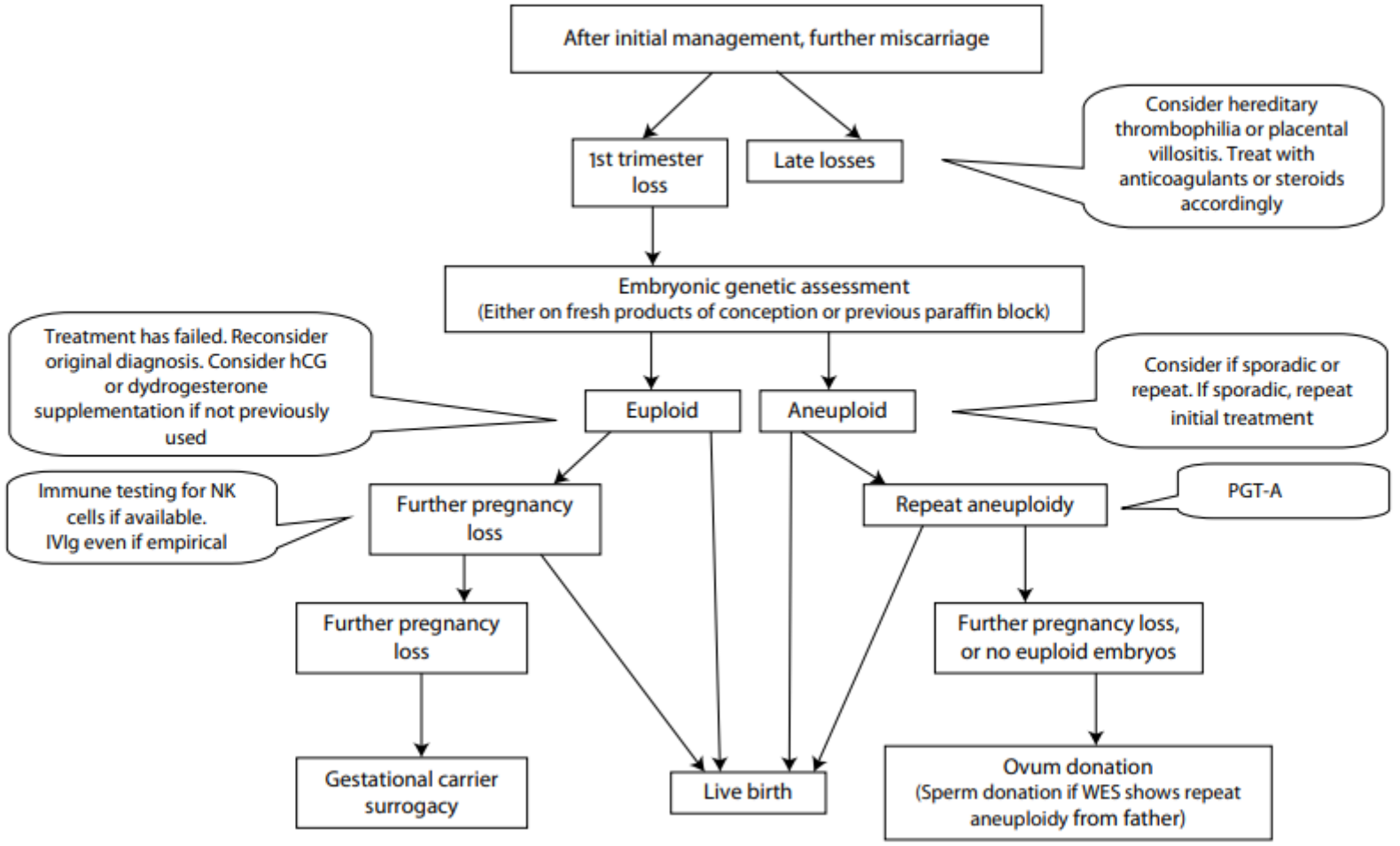

FIGURE 19.4 Flowchart for resistant patients.

Poor Prognosis Patients

The author defines these patients as those with five or more consecutive miscarriages. Saravelos and Li [4] classify these patients as Type 2 RPL. They have been poorly described in the literature and have formed the subjects of few trials. These patients constitute approximately 30% of the patients in our service. However, their proportion will be less in patients in centers using the ASRM or ESHRE definition of RPL as two or more miscarriages. Poor prognosis patients have usually had all the investigations and empirical treatments available. Hormone supplements, anticoagulants, hysteroscopic surgery, and often in vitro fertilization have been tried. In addition, there may be APS patients who have failed treatment and patients who continue miscarrying after surgery for uterine anomalies. However, most of these patients have not had fetal genetic analysis performed. After five or more miscarriages, the chance of fetal chromosomal aberrations is less than after three miscarriages. In poor prognosis patients, it is possible to retrieve histological specimens of previous miscarriages; either fixed slides or paraffin blocks can be used for comparative genetic hybridization (CGH) or next-generation screening (NGS) [35,36]. If one of the embryos is aneuploid, PGT-A should be considered. If, however, the embryo is euploid, PGT-A will not lead to a live birth. Our approach in these patients is to perform controversial testing and treatment such as immune testing.

Comparative Study > PLoS One. 2015 Jun 17;10(6):e0129958. doi: 10.1371/journal.pone.0129958. eCollection 2015.

Preimplantation Genetic Diagnosis and Natural Conception: A Comparison of Live Birth Rates in Patients with Recurrent Pregnancy Loss Associated with Translocation

Shinichiro Ikuma [1], Takeshi Sato [2], Mayumi Sugiura-Ogasawara [2], Motoi Nagayoshi [3], Atsushi Tanaka [3], Satoru Takeda [4]

After genetic counseling, 52 patients who desired natural conception and 37 patients who chose PGD were matched for age and number of previous miscarriages and these comprised the subjects of our study. PGD was performed by means of fluorescence in situ hybridization analysis. The live birth rates on the first PGD trial and the first natural pregnancy after ascertainment of the carrier status were 37.8% and 53.8%, respectively (odds ratio 0.52, 95% confidence interval 0.22-1.23). Cumulative live birth rates were 67.6% and 65.4%, respectively, in the groups undergoing and not undergoing PGD. The time required to become pregnancy was similar in both groups. PGD was found to reduce the miscarriage rate significantly. The prevalence of twin pregnancies was significantly higher in the PGD group. The cost of PGD was $7,956 U.S. per patient

Review > Reprod Biomed Online. 2018 Jun;36(6):677-685. doi: 10.1016/j.rbmo.2018.03.005. Epub 2018 Mar 15.

Does preimplantation genetic diagnosis improve reproductive outcome in couples with recurrent pregnancy loss owing to structural chromosomal rearrangement? A systematic review

Mahmoud Iews [1], Justin Tan [2], Omur Taskin [2], Sukainah Alfaraj [2], Faten F AbdelHafez [3], Ahmed H Abdellah [4], Mohamed A Bedaiwy [5]

Meta-analysis was precluded owing to significant heterogeneity between studies. The primary outcome of interest was live birth rate (LBR), and a pooled total of 847 couples who conceived naturally had a LBR ranging from 25-71% compared with 26.7-87% among 562 couples who underwent IVF and PGD. Limitations of the study include lack of large comparative or randomized control studies. Patients experiencing RPL with structural chromosomal rearrangement should be counselled that good reproductive outcomes can be achieved through natural conception, and **that IVF-PGD should not be offered first-line, given the unproven benefits, additional cost and potential complications associated with assisted reproductive technology.**

تشکر از توجه شما