



Diminished Ovarian Reserve May Explain Otherwise Unexplained Recurrent Pregnancy Loss

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Abstract

Objective: To evaluate the prevalence of Diminished Ovarian Reserve (DOR) in unexplained Recurrent Pregnancy Loss (RPL) patients.

Methods: Prospective cohort study including 264 patients with recurrent pregnancy loss, 87 with an identifiable cause and 177 patients with unexplained RPL, undergoing evaluation for at a University-affiliated private IVF clinic between January 1, 2011 and August 1, 2015.

Results: Of the 264 patients with recurrent pregnancy loss, 33% (N=87) had an identifiable cause for RPL after the ASRM-recommended evaluation was completed. The remaining 177 patients were considered to have unexplained RPL. A higher percentage of patients with unexplained RPL had DOR compared to patients with a known cause for RPL (48% vs. 29%, P=0.005). This finding was most significant in patients less than 38 years old compared to patients 38 years old and older (22% vs. 12%, P=0.02).

Conclusion: Diminished ovarian reserve is associated with RPL in many patients with otherwise unexplained RPL. This relationship may be explained by the high risk of aneuploidy miscarriage with DOR. This association of DOR with unexplained RPL is strongest in patients less than 38 years old. Providers should consider adding ovarian reserve testing to their evaluation of RPL patients to guide counseling for treatment options.

Introduction

Spontaneous pregnancy loss is the most common complication of pregnancy with an estimated 8-20% of clinically recognized pregnancies ending in miscarriage [1-3]. The risk of miscarriage increases with age such that a woman's chance of miscarriage at age 35 increases to 20% and by age 40 reaches 40% [4]. Recurrent Pregnancy Loss (RPL) is less common, and it is estimated that only 2% of women will experience two consecutive pregnancy losses, while less than 1% of women will experience three or more consecutive pregnancy losses [5].

The most common cause of first-trimester miscarriage is aneuploidy in the embryo [6], and the risk of aneuploidy in miscarriages increases with a woman's age [7]. This increased risk with age is most likely secondary to a higher percentage of aneuploid pregnancies with age [8]. Similarly, women with Diminished Ovarian Reserve (DOR) have a higher percentage of aneuploid embryos [9]. Further, one study evaluating the use of In Vitro Fertilization (IVF) with pre implantation genetic or chromosomal screening showed women with DOR and RPL have a higher percentage of aneuploid embryos than expected at a younger age [10]. Despite this link the American Society for Reproductive Medicine, European Society of Human Reproduction and Embryology and American Congress of Obstetricians and Gynecologists do not currently recommend ovarian reserve testing as a part of the evaluation for RPL.

The current ASRM recommended workup for RPL includes: parental karyotype analysis, screening for antiphospholipid syndrome, uterine evaluation for anatomic abnormalities and screening for hormonal imbalances. After completion of this recommended work up, approximately 50% of patients with RPL still have no explanation for their RPL [11].

A link between DOR, egg quality, aneuploidy, miscarriage and RPL could provide an explanation for many of these unexplained RPL patients. The objective of our study was to evaluate the prevalence of DOR in unexplained RPL patients through a prospective cohort study.

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Table 1: Etiology of explained RPL.

Etiology RPL	Explained RPL Patients (N=87)
Balanced Translocation	3% (N=3)
Antiphospholipid Antibodies	26% (N=23)
Uterine Anatomic Factors	24% (N=21)
	15% Septum
	9% Intracavitary Lesion
Hormonal	47% (N=41)
	42% Thyroid
	3% Prolactin
	2% HbA1c

Materials and Methods

At a private, university-affiliated fertility center in Seattle, Washington a prospective cohort study was conducted. Patients included those presenting for RPL between January 1, 2011 and August 1, 2015. These patients were offered an evaluation, including both the standard ASRM recommended evaluation, and ovarian reserve testing. Institutional review board approval was obtained for the project.

Clinical miscarriage was defined as pregnancy loss before 20 weeks' gestation, diagnosed by ultrasound (gestational sac or fetal pole) or products of conception. Patient reported history and medical records were both used. RPL was defined as two or more clinical miscarriages in accordance with the ASRM definitions [12].

The ASRM recommended workup for RPL was performed, which included testing for hormonal conditions (TSH, prolactin, HbA1c), antiphospholipid antibodies, uterine cavity defect and parental chromosomal balanced translocation. Unexplained RPL was defined as patients without any of the above listed conditions.

Ovarian reserve testing included both serum Anti-Mullerian Hormone (AMH) levels and cycle day 2 or 3 serum Follicle-Stimulating Hormone (FSH) and Estradiol (E_2). FSH and E_2 were measured by electrochemiluminescent immunoassay. AMH was measured with an ELISA (Gen II ELISA reference A79765) [13,14]. DOR was defined as FSH was ≥ 10 mIU/mL and/or their AMH level was < 1 ng/mL. Antral follicle count was not used as a measure of ovarian reserve in this study given its subjective nature in measurement and previous studies showing a close correlation between antral follicle count and serum AMH [15].

Data were analyzed using student T test and Chi square tests when appropriate and a P value of < 0.05 was considered to be statistically significant.

Results and Discussion

All patients presenting to our clinic from January 1, 2011 to August 1, 2015 were screened for inclusion. A total of 264 patients had two or more clinical miscarriages and received both ASRM evaluation for RPL and ovarian reserve testing.

Of eligible patients, a cause for RPL was found in 33% of patients (N=87). Of these positive findings, 47% of patients had hormonal conditions (42% thyroid, 3% prolactin, and 2% elevated HbA1C), 26% of patients tested positive for antiphospholipid antibodies, 24% of patients had a uterine anatomic factor (15% partial septum and 9% other intracavitary lesion), 3% of patients had a balanced

Table 2: Explained vs. Unexplained RPL patient characteristics.

	Explained RPL Patients n=87	Unexplained RPL Patients n=177	P-value
Age	35.2 (28-43)	36.4 (28-44)	0.06
BMI	23.6 (18-32.3)	22.6 (18.3-33.4)	0.07
No. of clinical miscarriages	2.5 (2-5)	2.7 (2-5)	0.8
History of aneuploid loss	18%	22%	0.4
%Prior Live Births	38%	52%	0.07
%Patients with FSH>10	26%	33%	0.2
%Patients with AMH <1.0	11%	32%	0.002
% Patients with DOR*	29%	48%	P=0.005

*DOR defined as FSH > 10 and/or AMH < 1.0 .

translocation, and 9% of patients had more than one positive finding (Table 1).

Clinical characteristics are provided in Table 2, with no statistically significant difference between ages, BMI, history of aneuploid loss or prior live birth in patients with explained and unexplained pregnancy loss.

Of the 67% of patients (N=177) with unexplained RPL, a higher percentage of patients had labs consistent with DOR. A greater percentage of unexplained RPL patients had an AMH level less than 1.0 ng/ml compared to patients with a known cause of RPL (32% vs. 11%). The prevalence of DOR was increased in the unexplained RPL group compared to patients with explained RPL when DOR was defined as FSH ≥ 10 mIU/mL and/or AMH level was < 1 ng/mL (48% vs. 29%, $p=0.005$).

The percentage of patients with DOR was higher in unexplained RPL patients compared to explained RPL patients across age groups but the difference was most significant in patients less than 38 years old (22% vs. 12%). In patients age 38 and older, the percentage of DOR was still higher in unexplained RPL patients compared to explained RPL patients but not significantly higher (58% vs. 51%) (Table 3).

While it is known that the most common cause of first-trimester miscarriage is aneuploidy in the embryo, and that women have a higher percentage of aneuploid embryos with increasing age, to our knowledge this is the first study to show that DOR, especially at younger ages, is associated with unexplained RPL.

Patients and clinicians alike find a lack of explanation for RPL challenging. Adding ovarian reserve testing to the workup of these patients would not only provide insight into the likely association of aneuploidy, DOR, and RPL for many patients, but would also help guide management and counseling early in the process. IVF with Chromosomal Screening (CS) of embryos has been proposed as a treatment option for patients with unexplained RPL [16] in the setting of the known high incidence of aneuploidy in products of conception from first-trimester miscarriage [11,18,19]. There are a number of studies which have shown known euploid embryo transfers are associated with a higher success rate and decreased risk of miscarriage for age [19-21]. Patients and providers alike can be focused on IVF with CS as a treatment option for RPL but success rates are significantly lower in patients with DOR.

Given the high costs of IVF, ovarian reserve testing in RPL patients would allow clinicians to more appropriately counsel

Table 3: Percentage of patients with DOR* according to Age.

Age (y)	Explained RPL (%) n=87	Unexplained RPL (%) N=177	P-Value
<35	5	12	0.04
35-37	15	28	0.01
38-40	45	51	0.3
41+	55	65	0.09

*DOR defined as FSH >10 and/or AMH<1.0

patients considering IVF on the utility of chromosomal screening and their overall estimated chances for success. Those patients with recurrent RPL and DOR are not only less likely to respond well to IVF medications, but also less likely to have a euploid embryo for transfer. Patients with significant DOR should be counseled about the limitations of autologous IVF and consider expectant management and alternative family building options like donor egg or adoption.

The association of DOR in unexplained RPL at younger ages is of interest. RPL may be considered an early warning sign of DOR, poor egg quality, and a shorter fertility potential. Regardless of use of IVF with CS as a treatment option for couples with RPL, the knowledge of DOR early in the process will help providers counsel patients thoroughly on their options.

Limitations of our study include patient population size. Given that DOR testing is not a routine part of the workup in RPL patients; a larger patient population could not be studied. If DOR testing becomes a routine part of the workup for unexplained RPL, it will be possible to further evaluate the implications of DOR in RPL patients with respect to optimal treatment options and IVF success rates. While DOR tests certainly add to the cost of an already expensive process, it may expedite treatment and ultimately decrease time and cost spent on treatments less likely to result in a successful pregnancy. Additionally, our percentage of unexplained RPL was a bit greater than previous studies which show a rate of about 50% [11]. This again, may be due to our lower sample size, or perhaps an older patient population than previously studied.

ASRM does not currently recommend ovarian reserve testing as a part of the evaluation for RPL. Our study found DOR in a significantly higher percentage of patients with unexplained RPL compared to explain RPL. This association is especially strong in patients less than 38 years old. This relationship may be explained by an associated between DOR, poor egg quality, aneuploidy, miscarriage, and RPL. Providers should consider adding ovarian reserve testing early in their evaluation of RPL patients to not only give insight into a possible cause but early guidance into treatment options.

References

- Regan L, Rai R. Epidemiology and the medical causes of miscarriage. *Baillieres Best Pract Res Clin Obstet Gynaecol.* 2000;14(5):839-54.
- Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. *N Engl J Med.* 1988;319(4):189-94.
- Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. *Fertil Steril.* 2003;79(3):577-84.
- Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *BMJ.* 2000;320:1708.
- Salat-Baroux J. *Reprod Nutr Dev.* 1988; 28:1555.
- Practice Committee Opinion of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril.* 2012;98(5):1103-11.
- Marquard K, Westphal L, Milki A, Lathi R. Etiology of recurrent pregnancy loss in women over the age of 35 years. *Fertil Steril.* 94(4):1473-7.
- Demko ZP, Simon AL, McCoy RC, Petrov DA, Rabinowitz M. Effects of maternal age on euploidy rates in a large cohort of embryos analyzed with 24-chromosome single-nucleotide polymorphism-based preimplantation genetic screening. *Fertil Steril.* 2016;105(5):1307-13.
- Katz-Jaffe MG, Surrey ES, Minjarez DA, Gustofson RL, Stevens JM, Schoolcraft WB. Association of abnormal ovarian reserve parameters with a higher incidence of aneuploidy blastocysts. *Obstet Gynecol.* 2013;121(1):71-7.
- Shahine LK, Marshall L, Lamb JD, Hickok LR. Higher rates of aneuploidy in blastocysts and higher risk of no embryo transfer in recurrent pregnancy loss patients with diminished ovarian reserve undergoing in vitro fertilization. *Fertil Steril.* 2016;106(5):1124-28.
- Stephenson MD. Frequency of factors associated with habitual abortion in 197 couples. *Fertil Steril.* 1996;66(1):24-9.
- Practice Committee Opinion of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. *Fertil Steril.* 2013;99(1):63.
- Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests predicting ovarian reserve and IVF outcome. *Hum Reprod Update.* 2006;12(6):685-718.
- Han X, McShane M, Sahertian R, White C, Ledger W. Pre-mixing serum samples with assay buffer is a prerequisite for reproducible anti-Mullerian hormone measurement using the Beckman Coulter Gen II assay. *Hum Reprod.* 2014;29(5):1042-8.
- Broer S, Mol B, Hendriks D, Broekmans F. The role of anti-Mullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. *Fertil Steril.* 2009;91(3):705-14.
- Munné S, Chen S, Fischer J, Colls P, Zheng X, Stevens J, et al. Preimplantation genetic diagnosis reduces pregnancy loss in women aged 35 years and older with a history of recurrent miscarriages. *Fertil Steril.* 2005; 84(2):331-5.
- Daniely M, Aviram-Goldring A, Barkai G, Goldman B. Detection of chromosomal aberration in fetuses arising from recurrent spontaneous abortion by comparative genomic hybridization. *Hum Reprod.* 1998;13(4):805-9.
- Carp H, Toder V, Aviram A, Daniely M, Mashiach S, Barkai G. Karyotype of the abortus in recurrent miscarriage. *Fertil Steril.* 2001;75(4):678-82.
- Garrisi J, Cohen J, Ferry KM, Colls P, Garrisi MG, Munné S. Preimplantation genetic diagnosis (PGD) effectively reduces idiopathic Recurrent Pregnancy Loss (RPL) among patients with up to five previous miscarriages after natural conception. *Fertil Steril.* 2007;88(1):S85.
- Munné S, Fischer J, N-neka G, Escudero T, Zheng X, Colls P. Preimplantation genetic screening for recurrent pregnancy loss. *Fertil Steril.* 2008;90:S24.
- Grifio J, Ghadir S, Kaplan B, Laskin C, Glassner M, Munné S. Significant decrease in miscarriages after preimplantation genetic diagnosis (PGD) for recurrent pregnancy loss using array comparative genome hybridization (Array CGH). *Fertil Steril.* 2011;96:S23.