

Manuscript version: Author's Accepted Manuscript

The version presented in WRAP is the author's accepted manuscript and may differ from the published version or Version of Record.

Persistent WRAP URL:

<http://wrap.warwick.ac.uk/130151>

How to cite:

Please refer to published version for the most recent bibliographic citation information. If a published version is known of, the repository item page linked to above, will contain details on accessing it.

Copyright and reuse:

The Warwick Research Archive Portal (WRAP) makes this work by researchers of the University of Warwick available open access under the following conditions.

© 2019 Elsevier. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International <http://creativecommons.org/licenses/by-nc-nd/4.0/>.



Publisher's statement:

Please refer to the repository item page, publisher's statement section, for further information.

For more information, please contact the WRAP Team at: wrap@warwick.ac.uk.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

Running title: Ovarian reserve in recurrent pregnancy loss

Title: Diminished ovarian reserve in recurrent pregnancy loss: a systematic review and meta-analysis

Sarah J Bunnewell BSc^{1†}, Emma R Honess BSc^{1†}, Amar M. Karia MBBS^{1,2}, Stephen D. Keay MD^{1,2}, Bassel H. Al Wattar PhD^{1,2,3}, Siobhan Quenby PhD^{1,2}

[†]The authors consider that the first two authors should be regarded as joint First Authors

¹Warwick Medical School, University of Warwick, Coventry, UK, CV4 7AL

²University Hospitals Coventry and Warwickshire, Coventry, UK, CV2 2DX

³Women’s Health Research Unit, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK, E1 2AB

Corresponding Author:

Dr.Bassel H.Al Wattar - Warwick Medical School, University of Warwick, Coventry, UK, CV4 7AL - E-Mail: dr.basselwa@gmail.com

25 **Capsule:** Our review of 15 studies suggests an association between diminished ovarian reserve
26 and recurrent pregnancy loss. There is a need to evaluate the best prognostic tools for diminished
27 ovarian reserve.

28 **Abstract (250)**

29 **Objective:** To evaluate the association between Diminished Ovarian Reserve (DOR) in women
30 at risk of Recurrent Pregnancy Loss (RPL) using Ovarian Reserve Tests (ORTs)

31 **Design:** Systematic review and meta-analysis

32 **Setting:** N/A

33 **Patient(s):** Women with history of RPL

34 **Intervention(s):** We systematically reviewed major electronic databases (MEDLINE, EMBASE,
35 Web of Science and Scopus) until May 2019 for studies that evaluated the incidence of DOR in
36 women with RPL. We assessed study quality using the Newcastle-Ottawa Scale and meta-
37 analyzed data using a random-effect model.

38 **Main Outcome Measure(s):** Association between RPL and DOR

39 **Results:** We included fifteen studies (n=3082women) reporting on six ORTs (AMH, AFC, FSH,
40 LH, Estradiol, FSH:LH ratio). More women with RPL seemed to have DOR compared to those
41 with non-RPL as measured by low AMH levels (OR 2.77, 95%CI 1.41-5.46, $p=0.03$, $I^2=0\%$) and
42 AFC (OR 2.45 95%CI 1.16-5.19, $p=0.02$, $I^2=59\%$). Women with unexplained RPL also seemed
43 to have a higher association with DOR compared to those with RPL of known aetiology,
44 measured by low AMH levels (OR 3.23 95%CI 1.81-5.76, $p<0.0001$, $I^2=0\%$). No statistically
45 significant differences were found in the levels of any of the remaining ORTs between those
46 groups of women.

47 **Conclusions:** There is an apparent association between diminished ovarian reserve and recurrent
48 pregnancy loss. Low AMH and AFC levels could predict higher odds for pregnancy loss but
49 more studies are needed to evaluate their prognostic value in the management of women with
50 recurrent pregnancy loss.

51

52 **Systematic review registration:** Prospero CRD42018114673

53 **Keywords:** Recurrent pregnancy loss, recurrent miscarriage, ovarian reserve, systematic review

54 **Introduction**

55 Recurrent Pregnancy Loss (RPL) affects 1-2% of women of reproductive age (1) and contributes
56 to long-term adverse pregnancy outcomes in affected couples.(2) A clear aetiology cannot be
57 determined in up to 50% of cases.(3,4) The advent of microarray analysis of miscarried tissue
58 can help to determine between normal and abnormal pregnancies with up to 95% of couples
59 being given a cause for their pregnancy losses.(5) Abnormal pregnancies conceived with an
60 abnormal or low-quality oocytes, which is more common with advancing maternal age, could be
61 a potential contributing factor to RPL in this group of women.(6) Evaluating ovarian reserve
62 directly could, therefore, help to predict the reproductive potential and optimize the care
63 provision for women at high risk of RPL.(7)

64

65 Various biochemical and sonographic tests have been developed to quantitatively assess the
66 ovarian reserve, predominantly for women undergoing assisted conception, including Anti-
67 Müllerian Hormone (AMH), basal Follicle Stimulating Hormone (FSH), basal Luteinising
68 Hormone (LH), FSH:LH ratio, basal Estradiol (E2) and Antral Follicle Count (AFC).(8)

69 However, there is uncertainty on the ability of these tests to evaluate the quality of remaining
70 oocytes in addition to their quantity. Their predictive value for reproductive outcomes of women
71 with diminished ovarian reserve (DOR) also remains imprecise.(1)

72

73 We conducted a systematic review of the literature to evaluate the evidence on the association
74 between RPL and DOR and evaluate the use of ORTs in this context.

75

76 **Materials and methods**

77 We conducted this systematic review using a prospectively registered protocol (PROSPERO
78 CRD42018114673) and reported in line with the PRISMA statement.

79

80 *Search Strategy*

81 We searched major electronic databases (MEDLINE, EMBASE, Web of Science and Scopus)
82 from inception until May 2019 for all primary studies evaluating the association between DOR
83 and RPL in women who underwent static ovarian reserve testing using any identified marker.
84 We used Medical Subject Headings (MeSH) terms for ‘recurrent pregnancy loss’ and ‘ovarian
85 reserve tests’ and combined them with AND or OR Boolean operators. We did not apply any
86 search filters or limitations. We conducted forward and backward citation tracking of included
87 articles to identify any articles not captured in our electronic search. Non-English language
88 publications were translated if deemed relevant. Our exclusion criteria were: studies including
89 women with a medical condition or treatment known to be associated with RPL or ORTs; oocyte
90 donation recipients; interventional studies; animal studies; case reports; commentaries; review
91 articles and editorials.

92

93 *Study Selection and Inclusion Process*

94 We performed a two-stage screening and inclusion process. Firstly, two independent reviewers
95 (EH and SB) screened the titles and abstracts of potentially relevant citations to assess eligibility.
96 In the second stage, we obtained full articles of selected citation and evaluated them against our
97 inclusion criteria. Any disagreement was resolved by discussion with a third reviewer (BHA).

98

99 *Data Extraction and Quality assessment*

100 We extracted data in duplicate onto an electronic database piloted among co-authors. We
101 collected data on the following: name of authors, year of publication, country of publication,
102 study population characteristics, cut-off values for diminished ovarian reserve, ovarian reserve
103 test values in each group.

104 We used the Newcastle-Ottawa Scale (NOS)(9) to assess the quality of the included studies in
105 duplicate by two reviewers (EH and SB). Studies were awarded a maximum of four stars for
106 selection, two for comparability and three for assessment of outcomes. Studies that scored four
107 stars for selection, two stars of comparability and three stars for assessment of outcomes were
108 considered to be of high quality. Scores of one star or less for selection, comparability or
109 outcome assessment were considered to be of low quality. Any other score combinations were
110 considered of medium quality. We did not perform a funnel plot analysis due to the small
111 number of studies included.

112

113 *Statistical analysis*

114 We reported on dichotomous outcomes using Odd Ratio (OR) where possible. Studies reporting
115 on differences in mean values were included in the systematic review but not in the quantitative
116 meta-analysis. We performed a direct comparison meta-analysis using a random effect model
117 and reported using OR and 95% Confidence Intervals (CI). We evaluated the heterogeneity in
118 included studies using I^2 statistics categorized as per the Cochrane Handbook thresholds to
119 ‘moderate’, ‘substantial’ or ‘considerable’. Sensitivity analysis was not conducted due to the
120 small number of included studies for each ovarian reserve test. All statistical analyses were
121 conducted in Microsoft Excel (Microsoft Excel v.2016, Microsoft Redmond, Washington) and
122 RevMan (Review Manager (RevMan). V5.3. Copenhagen: The Nordic Cochrane Centre, The
123 Cochrane Collaboration, 2014).

124

125 **Results**

126 *Characteristics of included studies*

127 Our search identified 2518 potentially relevant citations following deduplication. We assessed
128 148 full articles against our eligibility criteria and included 15 observational studies reporting on
129 3082 women and 6 ovarian reserve tests (AMH, FSH, Estradiol, LH, AFC and FSH:LH ratio).
130 (Table 1).

131 The majority of studies were case-control in design (12/15, 80.0%) and three studies were cohort
132 (20.0%). Nearly one-third of included studies were published in Europe (5/15, 33.3%) and a
133 quarter were published in North America (4/15, 26.7%). The majority were published in
134 specialist journals (12/15, 80.0%).

135

136 The definition of RPL in the inclusion criteria varied among included studies with the majority
137 defining RPL as three or more miscarriages (11/15, 73.3%) whilst 4 of the 15 studies (26.7%)
138 included women with two or more miscarriages. Seven studies included women specifically with
139 consecutive miscarriages (7/15, 46.7%). Ten studies specifically stated their participants had first
140 trimester (2/15, 13.3%) or <20-week gestation (8/15, 53.3%) pregnancy losses (Table 1). Ten
141 studies compared women with RPL to women without a history of RPL (non-RPL) (10/15,
142 63.3%) and five compared women with unexplained RPL (URPL) to those with explained RPL
143 (ERPL) (5/15, 33.3%). The average age of participants was 32.0 years in the RPL group, 32.4
144 years in the non-RPL group, 35.5 years in the URPL group and 34.3 years in the ERPL group.
145 The control group for non-RPL consisted of women who were in-clinic seeking contraception,
146 undergoing sterilization or receiving In Vitro Fertilization (IVF) on the basis of male factor

147 infertility with no history of miscarriage or history of RPL. One study described ‘no history of
148 RPL’ as women who had two or fewer previous miscarriages.(10)

149
150 The direct causes for ERPL in the included studies were: presence of thyroid peroxidase
151 antibodies (TPOab), uterine abnormalities, thrombophilic defects, antiphospholipid syndrome
152 (APLS), parental chromosomal abnormalities, thyroid abnormalities, diabetes mellitus (DM) and
153 ‘hormonal conditions’. Only six studies (6/15, 40.0%) reported a cut-off for defining DOR in
154 their cohort thus allowing quantitative meta-analyses of data (Figure 1).

155
156 *Quality of included studies*

157 The overall quality of the included studies was medium with the majority of studies showing
158 good quality for both population selection (12/15, 80.0%), and outcome assessment (13/15,
159 86.7%). There was poor quality in selecting appropriate comparison groups in over half of the
160 included studies (8/15, 53.3%), and only 4 studies showed good quality for their comparison
161 methods (26.7%). (Supplemental figure 1)

162
163 *AMH*

164 Women with RPL had lower levels of AMH suggesting an association with DOR in three studies
165 (7,10,11), however, this was not the case in two of the included studies with no significant
166 difference in AMH levels between RPL and non-RPL groups.(12,13) One study by *Pils et al*(14)
167 suggested lower AMH levels in women with URPL compared to ERPL (1.2 ng/mL [1.1; 2.7] vs.
168 2.0 ng/mL [1.1; 2.7], p=0.037), however such association was not confirmed in the study by
169 *Bliddal et al.*(15)

170 We pooled data from two studies reporting on DOR with AMH ≤ 1 ng/mL (n=313 women).(7,11)
171 Overall there was higher OR of 2.77 for DOR in the RPL group (95%CI 1.41-5.46, $p=0.03$,
172 $I^2=0\%$) (Figure 2a). Similarly, a meta-analysis showed higher odds for DOR in women with
173 URPL compared to ERPL (OR 3.23, 95%CI 1.81-5.76, $p<0.0001$, $I^2=0\%$) (n=772 women)
174 (Figure 2b).(15–17)

175

176 *AFC*

177 Two studies reported on the association between DOR defined by an AFC ≤ 7 in RPL and non
178 RPL women.(7,11) Pooled data of 313 women showed significantly higher odds for DOR in
179 women with RPL compared to non-RPL (OR 2.45, 95%CI 1.16, 5.19, $p=0.02$, $I^2=59\%$) (Figure
180 3).

181

182 *FSH*

183 Overall there was no clear difference in the levels of FSH between women with RPL and non-
184 RPL in three of the included studies,(11,18,19) one study suggested higher levels (7) and one
185 suggested lower levels in the RPL group.(13) We pooled the data from two studies (n=313
186 women) (7,11) reporting on DOR with an FSH ≥ 11 U/L in RPL versus non-RPL women and
187 found higher OR of 2.05 (95%CI 0.36-11.55, $p=0.42$) but there was high heterogeneity among
188 included studies ($I^2=73\%$). (Supplemental figure 2a) Data from three studies (15–17) revealed no
189 significant association with DOR reported by high FSH in women with URPL compared to
190 ERPL (OR=1.85, 95%CI 0.72, 4.74, $p=0.20$, $I^2=39\%$) (n=359 women) (Supplemental figure 2b).
191 The FSH:LH ratio evaluated by two studies (7,11) was not statistically different between RPL
192 and non-RPL women.

193

194 *LH*

195 Overall there was no strong evidence of higher LH values associated with RPL with only one
196 (18) of three studies (7,19) included suggesting a higher average compared to women with non-
197 RPL (4.5 ± 0.2 vs. 3.0 ± 1.4 IU/ml, $p < 0.001$). *Regan et al* (20) used a threshold of $LH \geq 10$ IU/L
198 to define DOR and suggested a higher association with RPL (9/30, 30.0%) compared to non-RPL
199 women (1/17, 5.9%) ($p < 0.05$). Only one study (14) evaluated LH levels between women with
200 URPL and ERPL suggesting no significant differences.

201

202 *Estradiol*

203 There were no significant differences in levels of Estradiol between women with RPL and non-
204 RPL in six of the included studies.(7,11,18,19,21,22) Using a cut-off of ≥ 60 nmol/L, those
205 findings were supported by our meta-analysis using data from two studies (n=313 women) (7,11)
206 with an OR of 1.94 (95%CI 0.16- 3.48, $p = 0.60$, $I^2 = 94\%$) (Supplemental figure 3). Similarly, no
207 difference was found in Estradiol levels between women with URPL and ERPL in two
208 studies.(14,23)

209

210 **Discussion**

211 *Summary of findings*

212 In this systematic review, we highlight a potential association between diminished ovarian
213 reserve and higher odds for RPL, especially in women with URPL. We aimed to evaluate the
214 best ORT to screen for such association but due to the lack of standardized reporting thresholds,
215 we are unable to make firm conclusions. However, the use of AMH and AFC seems to offer the
216 best prognostic value which is consistent with their established convenience and reliability in
217 clinical practice.(24)

218

219 *Strengths and Limitations*

220 We conducted our review using a prospectively registered protocol and employing a
221 comprehensive search strategy. We included all relevant study designs and evaluated the risk of
222 bias in included studies in duplicate. We reported on all included studies and used a random
223 effect model to pool data where possible.

224

225 Our findings are not without limitations; although we identified a relatively large number of
226 studies reporting on the association between ovarian reserve and RPL, there were considerable
227 variations in population characteristics, test thresholds and reported outcomes which limited our
228 ability to synthesis data meaningfully. Women with RPL represent a heterogeneous group;
229 without a unanimous definition for RPL cases or the non-RPL comparator groups used across the
230 studies included in this review, the possibility of contamination between groups must be
231 considered.(25) Our meta-analyses consisted primarily of data from a small number of studies
232 which limits the value of pooling data, thus, the findings should be interpreted with caution. We
233 were unable to adjust for certain important effect modifiers such as age, ethnicity and the
234 biochemical assays used to measure ORTs which could affect our findings. These are especially
235 relevant to the prognostic value of AMH and AFC as they tend to decrease with advancing
236 maternal age. Due to the small number of studies and limited information reported, a meta-
237 regression was not possible.

238

239 *Wider implications and future research*

240 Care for women with RPL remains a clinical challenge due to the limited range of available
241 screening and treatment modalities.(26) The heterogeneous pathophysiology of this group of

242 women limits the accuracy of prognostic screening to plan future treatment options. The advent
243 of available array techniques for analysing miscarried tissue means an increasing awareness of
244 the contribution of abnormal pregnancies to RPL so that specific investigations can be offered to
245 those with higher risk of conceiving an abnormal pregnancy. The association between advancing
246 maternal age, decreasing oocyte numbers, and the risk for aneuploidy RPL is well
247 established.(27,28) Still, the efficacy of available treatment options such as assisted reproduction
248 technologies (ARTs) including, preimplantation genetic testing for aneuploidy (PGT-A) and
249 oocyte donation, in the management of RPL remains unclear.(29) Evaluating DOR and the
250 associated risk of RPL could help this group of high-risk women and their caring health
251 professionals to weigh in the available treatment options and to optimize their care.

252

253 To date, there is still no universally accepted definition of DOR, which significantly hinders the
254 potential to synthesise evidence and improve the care of women with RPL.(30) In this review,
255 we also highlight the high variation in outcomes reporting which also reduced our ability to
256 synthesise meaningful conclusions. Developing a core set of outcomes for RPL research and
257 standardizing their definitions would help to resolve this issue.(31)

258

259 Both AMH and AFC have been used to predict various reproductive outcomes in couples
260 seeking fertility treatments such as predicting IVF success (32), live birth (33), and response to
261 ovulation stimulation.(34) Our findings supporting their potential value to advice on the
262 treatment options for women at risk of RPL fit with the overall prognostic value of these tests.
263 Still, our estimates are imprecise due to several limitations such as the variations in available
264 diagnostic essays (35), sonographic limitations (36), and the natural decline of these markers
265 with age.(37) Thus future studies should adjust for these important effect modifiers. We only

266 captured evidence on the use of static ORTs. Several other static tests are used in practice such as
267 Inhibin B, ovarian volume and ovarian vascularity but we could not identify any relevant studies
268 to evaluate their use in the context of RPL. Dynamic ORTs, such as Clomiphene Citrate
269 Challenge Test (CCCT) and Gonadotrophin-releasing hormone Agonist Stimulation Test
270 (GAST), which assess ovarian responses to exogenous stimulation, could be helpful to screen for
271 DOR in women at risk of RPL, but future studies are needed to evaluate their prognostic value.
272 Future large prospective cohort studies are also needed to evaluate the role of ORT screening for
273 subfertility in clinical practice and to identify the test with the best cost-effective qualities.

274

275 **Conclusion**

276 There is an apparent association between diminished ovarian reserve and recurrent pregnancy
277 loss. Low AMH and AFC levels could predict higher odds for pregnancy loss but more studies
278 are needed to evaluate their prognostic value in the management of women with recurrent
279 pregnancy loss.

280

281 **Acknowledgements:** None

282 **Funding:** None

283 **Declaration of interest:** None

284 **Contribution to authorship:** SB and EH wrote the study protocol, conducted the search, extracted
285 data, and conducted the primary analysis, BHA oversaw the study conduct and finalised the analysis, SQ
286 conceived the idea and oversaw the study conduct, AK and SK contributed to data curation, all authors
287 contributed critically to the final manuscript.”

288

289 **References**

- 290 1. RPL EGG on, Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al.
291 ESHRE guideline: recurrent pregnancy loss [Internet]. 2018;Available from:
292 <https://www.eshre.eu/-/media/sitecore-files/Guidelines/Recurrent-pregnancy-loss/ESHRE->
293 [RPL-](https://www.eshre.eu/-/media/sitecore-files/Guidelines/Recurrent-pregnancy-loss/ESHRE-)
294 [Guideline_27112017_FINAL_v2.pdf?la=en&hash=34DB7D51CF98BFC3DA48FAAA7E](https://www.eshre.eu/-/media/sitecore-files/Guidelines/Recurrent-pregnancy-loss/ESHRE-)
295 [7DAED670BA6A83](https://www.eshre.eu/-/media/sitecore-files/Guidelines/Recurrent-pregnancy-loss/ESHRE-)
- 296 2. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome
297 following idiopathic recurrent miscarriage. *Hum Reprod* 1999;14:2868–71.
- 298 3. Tho PT, Byrd JR, McDonough PG. Etiologies and subsequent reproductive performance
299 of 100 couples with recurrent abortion. *Fertil Steril* 1979;32:389–95.
- 300 4. Jaslow CR, Carney JL, Kutteh WH. Diagnostic factors identified in 1020 women with two
301 versus three or more recurrent pregnancy losses. *Fertil Steril* 2010;93:1234–43.
- 302 5. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with
303 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of
304 pregnancy loss in over 90% of patients. *Hum Reprod* 2018;33:579–87.
- 305 6. Tatone C, Amicarelli F, Carbone MC, Monteleone P, Caserta D, Marci R, et al. Cellular
306 and molecular aspects of ovarian follicle ageing. *Hum Reprod Update* 2008;14:131–42.
- 307 7. Atasever M, Soyman Z, Demirel E, Gencdal S, Kelekci S. Diminished ovarian reserve: is
308 it a neglected cause in the assessment of recurrent miscarriage? A cohort study. *Fertil*
309 *Steril* 2016;105:1236–40.
- 310 8. Broekmans FJ, Kwee J, Hendriks DJ, Mol BW, Lambalk CB. A systematic review of tests
311 predicting ovarian reserve and IVF outcome. *Hum Reprod Update* 2006;12:685–718.
- 312 9. Wells G, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa

- 313 quality assessment scale cohort studies. 2015-11-19]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. 2014;
- 314
- 315 10. Schumacher BML, Jukic AMZ, Steiner AZ. Antimüllerian hormone as a risk factor for
316 miscarriage in naturally conceived pregnancies. *Fertil Steril* 2018;109:1065–71.
- 317 11. Yildirim GY, Celik HG, Koroglu N, Karakus E. Do ovarian reserve markers predict the
318 subsequent pregnancy outcomes in women with recurrent pregnancy loss? *Turkish J*
319 *Biochem* 2018;43:481–6.
- 320 12. Leclercq E, Pasquier E, Martelot M-TLE, Roche S, Bohec C, Collet PM. Is anti-müllerian
321 hormone a determinant in unexplained recurrent miscarriage? *Human Reproduction*. 2014.
322 p. 137.
- 323 13. Nonez H, Rodriguez-Purata J, Lee JA, Whitehouse MC, Slifkin R, Moschini RA, et al.
324 Aneuploidy rates are not increased in patients with recurrent pregnancy loss. *Fertil Steril*
325 2016;106:e106.
- 326 14. Pils S, Promberger R, Springer S, Joura E, Ott J. Decreased ovarian reserve predicts
327 inexplicability of recurrent miscarriage? A retrospective analysis. *PLoS One*
328 2016;11:e0161606.
- 329 15. Bliddal S, Nielsen HS, Hilsted L, Kolte AM, Larsen E NC. Thyroid peroxidase antibodies
330 and anti-mullerian hormone in 470 women with unexplained recurrent pregnancy loss. *Eur*
331 *Thyroid J* [Internet] 2018;7 (Supplem:41. Available from: [http://program.m-](http://program.m-anage.com/eta2018/en-GB/ProgramSearch/DownloadAbstractOfPresentation/353034)
332 [anage.com/eta2018/en-GB/ProgramSearch/DownloadAbstractOfPresentation/353034](http://program.m-anage.com/eta2018/en-GB/ProgramSearch/DownloadAbstractOfPresentation/353034)
- 333 16. Wald KA, Hickok LR, Marshall LA, Lamb JD, Shahine LK. Diminished ovarian reserve
334 may explain otherwise unexplained recurrent pregnancy loss. *Fertil Steril* 2017;107:e14.
- 335 17. Zolghadri J, Younesi M, Tabibi A, Khosravi D, Behdin S VH. Do patients with
336 unexplained and explained recurrent pregnancy loss suffer from diminished ovarian

- 337 reserve? Iran J Reprod Med [Internet] 10(SUPPL.1):3. Available from:
338 <http://journals.ssu.ac.ir/ijrmnew/article-1-333-en.pdf>
- 339 18. Mahdavi-pour M, Zarei S, Fatemi R, Edalatkhah H, Heidari-Vala H, Jeddi-Tehrani M, et
340 al. Polymorphisms in the estrogen receptor Beta Gene and the Risk of unexplained
341 recurrent spontaneous abortion. *Avicenna J Med Biotechnol* 2017;9:150.
- 342 19. Liu S, Wei H, Li Y, Huang C, Lian R, Xu J, et al. Downregulation of ILT 4+ dendritic
343 cells in recurrent miscarriage and recurrent implantation failure. *Am J Reprod Immunol*
344 2018;80:e12998.
- 345 20. Regan L, Owen EJ, Jacobs HS. Hypersecretion of luteinising hormone, infertility, and
346 miscarriage. *Lancet* 1990;336:1141–4.
- 347 21. Habara T, Nakatsuka M, Konishi H, Asagiri K, Noguchi S, Kudo T. Elevated blood flow
348 resistance in uterine arteries of women with unexplained recurrent pregnancy loss. *Hum*
349 *Reprod* 2002;17:190–4.
- 350 22. Carranza-Lira S, Blanquet J, Tserotas K, Calzada L. Endometrial progesterone and
351 estradiol receptors in patients with recurrent early pregnancy loss of unknown etiology-
352 preliminary report. *Med Sci Monit* 2000;6:759–62.
- 353 23. Trout SW, Seifer DB. Do women with unexplained recurrent pregnancy loss have higher
354 day 3 serum FSH and estradiol values? *Fertil Steril* 2000;74:335–7.
- 355 24. Tal R, Seifer DB. Ovarian reserve testing: a user’s guide. *Am J Obstet Gynecol*
356 2017;217:129–40.
- 357 25. Ogasawara M, Aoki K, Okada S, Suzumori K. Embryonic karyotype of abortuses in
358 relation to the number of previous miscarriages. *Fertil Steril* 2000;73:300–4.
- 359 26. El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet P-E.
360 Recurrent pregnancy loss: current perspectives. *Int J Womens Health* 2017;9:331.

- 361 27. Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in
362 women over the age of 35 years. *Fertil Steril* 2010;94:1473–7.
- 363 28. Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new
364 model of reproductive aging: the decline in ovarian non-growing follicle number from
365 birth to menopause. *Hum Reprod* 2008;23:699–708.
- 366 29. Murugappan G, Shahine LK, Perfetto CO, Hickok LR, Lathi RB. Intent to treat analysis of
367 in vitro fertilization and preimplantation genetic screening versus expectant management
368 in patients with recurrent pregnancy loss. *Hum Reprod* 2016;31:1668–74.
- 369 30. Cohen J, Chabbert-Buffet N, Darai E. Diminished ovarian reserve, premature ovarian
370 failure, poor ovarian responder—a plea for universal definitions. *J Assist Reprod Genet*
371 2015;32:1709–12.
- 372 31. Khan K. The CROWN Initiative: journal editors invite researchers to develop core
373 outcomes in women’s health. *BJOG*. 2016;123 Suppl:103–4.
- 374 32. Broer SL, Mol BWJ, Hendriks D, Broekmans FJM. The role of antimüllerian hormone in
375 prediction of outcome after IVF: comparison with the antral follicle count. *Fertil Steril*
376 2009;91:705–14.
- 377 33. Iliodromiti S, Kelsey TW, Wu O, Anderson RA, Nelson SM. The predictive accuracy of
378 anti-Müllerian hormone for live birth after assisted conception: a systematic review and
379 meta-analysis of the literature. *Hum Reprod Update* 2014;20:560–70.
- 380 34. Nardo LG, Gelbaya TA, Wilkinson H, Roberts SA, Yates A, Pemberton P, et al.
381 Circulating basal anti-Müllerian hormone levels as predictor of ovarian response in
382 women undergoing ovarian stimulation for in vitro fertilization. *Fertil Steril*
383 2009;92:1586–93.
- 384 35. Li HWR, Ng EHY, Wong BPC, Anderson RA, Ho PC, Yeung WSB. Correlation between

385 three assay systems for anti-Müllerian hormone (AMH) determination. *J Assist Reprod*
386 *Genet* 2012;29:1443–6.

387 36. Hendriks DJ, Kwee J, Mol BWJ, te Velde ER, Broekmans FJM. Ultrasonography as a tool
388 for the prediction of outcome in IVF patients: a comparative meta-analysis of ovarian
389 volume and antral follicle count. *Fertil Steril* 2007;87:764–75.

390 37. Seifer DB, Baker VL, Leader B. Age-specific serum anti-Müllerian hormone values for
391 17,120 women presenting to fertility centers within the United States. *Fertil Steril*
392 2011;95:747–50.

393

394

395

396

397

398 **Figure legends:**

399 **Figure 1:** The selection and inclusion process for studies evaluating the association between
400 diminished ovarian reserve and recurrent pregnancy loss#

401 **Figure 2:** Meta-analysis evaluating the association between diminished ovarian reserve (DOR)
402 and recurrent pregnancy loss (RPL) using Anti-Mullerian Hormone levels (AMH)

403 **Figure 3:** Meta-analysis evaluating the association between diminished ovarian reserve (DOR)
404 defined using Antral Follicle Count (AFC) ≤ 7 in women with recurrent pregnancy loss (RPL)
405 compared to non-RPL.

406 **Supplemental figure 1:** The quality of included studies evaluating the association between
407 diminished ovarian reserve and recurrent pregnancy loss assessed using the Newcastle-Ottawa
408 Scale.

409 **Supplemental figure 2:** Meta-analysis evaluating the association between diminished ovarian
410 reserve (DOR) and recurrent pregnancy loss (RPL) using Follicle stimulating hormone (FSH)

411 **Supplemental figure 3:** Meta-analysis evaluating the association between diminished ovarian
412 reserve (DOR) defined using Estradiol ≥ 60 nmol/L in women with recurrent pregnancy loss
413 (RPL) compared to non-RPL.