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Running title: Ovarian reserve in recurrent pregnancy loss

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

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

Abstract (250)

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

Design: Systematic review and meta-analysis

Setting: N/A

Patient(s): Women with history of RPL

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

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

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

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

Systematic review registration: Prospero CRD42018114673

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

Introduction

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

Various biochemical and sonographic tests have been developed to quantitatively assess the ovarian reserve, predominantly for women undergoing assisted conception, including Anti-Müllerian Hormone (AMH), basal Follicle Stimulating Hormone (FSH), basal Luteinising Hormone (LH), FSH:LH ratio, basal Estradiol (E2) and Antral Follicle Count (AFC).(8) However, there is uncertainty on the ability of these tests to evaluate the quality of remaining oocytes in addition to their quantity. Their predictive value for reproductive outcomes of women with diminished ovarian reserve (DOR) also remains imprecise.(1)

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

Materials and methods

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

Search Strategy

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

Study Selection and Inclusion Process

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

Data Extraction and Quality assessment

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

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

Statistical analysis

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

Results

Characteristics of included studies

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

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

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

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

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

Quality of included studies

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

AMH

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

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

AFC

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

FSH

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

LH

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

Estradiol

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

Discussion

Summary of findings

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

Strengths and Limitations

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

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

Wider implications and future research

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

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

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

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

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

Conclusion

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

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Declaration of interest: None

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

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Figure legends:

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

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

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

Supplemental figure 1: The quality of included studies evaluating the association between dimineshed ovarian reserve and recurrent pregancny loss assessed using the Newcastle-Ottawa Scale.

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

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