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Chronic Endometritis in female reproduction. A meta-analysis

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Statement of the Problem: Chronic endometritis (CE) is a persistent inflammation of the endometrium, often resulting from an intrauterine infection caused by common bacteria as well as *Mycoplasma* e *Ureaplasma* spp. The actual impact of chronic endometritis (CE) on female reproduction is a still unresolved issue. The currently available studies on this matter differ regarding the definition of CE, the diagnostic methods of the condition and the reproductive disorders investigated and compared. Moreover, there are few studies in which the control population is represented by normally fertile women. The objective of this meta-analysis is to assess the possible role of CE in three major reproductive disorders: female infertility, recurrent implantation failure (RIF) and recurrent pregnancy loss (RPL).

Methods: The present meta-analysis has been carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA STATEMENT 2020) (1). A systematic search of the literature in english language from January 1,1990 to February 2, 2024 has been carried out on the following database sources: Pubmed, Scopus, Web of Science, ScienceDirect and Cochrane Library. For each of them two distinct search strings have been set, one for CE and RPL and an other one for CE, infertility and RIF. Combinations of relevant terms (MeSH) and key-words related to the exposition of the events of interest have been built up. Systematic reviews, meta-analyses, reviews, case reports, notes or letters, editorials, book chapters, erratums and conference abstracts were excluded. Only studies on humans were considered and those involving animals were excluded. Electronic searches and analysis of bibliographic lists were performed independently by the authors. These reviewers subsequently screened titles, abstracts, and full texts, according to the inclusion and exclusion criteria previously described. Any disagreements between the reviewers were resolved through mutual agreement. The Newcastle-Ottawa scale (NOS) for nonrandomized studies was used to evaluate the quality of the included studies (2). Quantitative analysis of the extracted data was conducted using RevMan 5.4 software. Study outcomes were expressed using an odds ratio (OR) with a 95% confidence interval (95% C.I.). A P value<0.05 was defined as indicative of a statistically significant difference in outcomes. Heterogeneity between studies was measured using the I² statistic. The degree of heterogeneity was considered low when I² is less than 30%, moderate if between 30% and 70% and high if greater 70%. If I² exceeded 70%, indicating high variability between studies, the data were not usable for meta-analysis. If the I² was between 30% and 70%, the choice model was random effects. Conversely, in the presence of I² lower than 30%, a fixed model was used.

Findings: Three thousand and four relevant publications have been found (Pubmed: 522, Scopus: 1.447, Web of Science: 692, ScienceDirect: 230, Cochrane Library: 113). After removing duplicates, the titles and abstracts of the remaining 1.511 documents were examined. Of these 1.511, 1.495 were excluded taking into account the imposed exclusion criteria, while 16 studies were pre-selected for inclusion. Further 7 studies were excluded for various reasons: lack of a control group composed by healthy fertile women, CE as a prerequisite for the selection of groups, lack of reported prevalence of CE in control group. Finally, a total of nine studies were included: four prospective cohort studies, one prospective and retrospective cohort study, two retrospective cohort studies and two case-control studies. Overall, the present meta-analysis involves a population of 1.038 women, including 185 suffering from infertility, 63 with repeated implantation failure, 489 diagnosed with RPL and 486 healthy fertile women (controls).

Cumulative results showed:

- 1. With regard to infertility:** A positive association between infertility and CE: a higher percentage of CE was found in infertile women (36/185 [19,46%]) compared to controls (14/180 [7,7%]), fixed effects model, OR: 2,96, 95% CI: 1.53-5.72, p<0.001, I² = 0% (2 studies);
- 2. With regard to RIF:** No association between RIF and CE, fixed effects model, OR: 1.10, 95% CI: 0.26-4.61, p = 0,90, I² = 0%; the prevalence of CE in women with RIF (4/63 [6.35%]) was not statistically different compared to controls (4/69 [5.8%]) (2 studies);

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3. **With regard to RPL:** A positive association between CE and RPL was found: a higher percentage of CE was found in women with RPL (184/ 489 [37.6%]) compared to controls (57/346 [16.4%]), fixed effects model, OR: 3.59, 95% CI: 2.46-5.24, $p < 0.00001$, $I^2 = 0\%$ (8 studies).

Conclusions and Significance

To our knowledge, the present study is the first meta-analysis carried out to investigate at the same time the prevalence of CE in infertility, RPL and RIF. The results of our study indicate that CE is more common on women with infertility and RPL compared to the control group. In contrast, no significant differences in the prevalence of CE were found between women with RIF and the control group. However, the limited number of studies and subjects involved, as well as the different diagnostic criteria of CE used in the different studies prevent drawing firm conclusions. There is urgent need to develop well-designed, controlled studies with adequate numbers of subjects involved, using uniform diagnostic criteria to definitely establish the actual role, as well as its clinical significance, of CE in female infertility, RIF and RPL.

Biography

Carlo Ticconi is Associate Professor of Obstetrics and Gynecology - Department of Surgery – University of Rome “Tor Vergata”, Rome, Italy. Currently he works at the University Hospital Policlinico Tor Vergata – Rome as Ob/Gyn, Department of Surgery, Section of Gynecology and Obstetrics Clinical experiences: delivery room and ward, general gynecology and obstetrics, gynaecological and obstetrical endocrinology, operative gynecology, recurrent pregnancy loss Areas of research interests: Female reproduction – Pregnancy and labor – Pregnancy complications – Recurrent Pregnancy Loss. Peer reviewer in more than 20 scientific journals in the area of Ob/Gyn. Author of 243 scientific publications (national and international).