Does an association exist between menstrual cycle length within the normal range and ovarian reserve biomarkers during the reproductive years? A systematic review and meta-analysis

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INTRODUCTION

Regular menstrual cycling during the reproductive years is an indicator of spontaneous ovulation but sometimes falsely perceived as an indicator of preserved fertility. In contrast, menstrual cycle shortening, a physiologic occurrence preceding the menopausal transition, is not usually perceived as an indicator of decreased ovarian reserve in the general population. The individual decrease in menstrual cycle length (MCL) might represent a sensitive biomarker of diminishing ovarian reserve. The aim of this systematic review and meta-analysis is to examine the possible association between MCL in regularly cycling women (21–35 days) and ovarian reserve tests (ORT), fecundability in natural cycles and IVF outcomes.

RESULTS

All prospective and retrospective studies exploring an association between MCL and proxies of ovarian reserve were included. The exclusions included studies of Polycystic ovary syndrome, ovarian failure, oral contraception treatment, prior chemotherapy and/or radiotherapy or ovarian surgery. Eleven studies were eligible for meta-analysis, including 12,031 women. The included studies had a low risk of bias.

Short MCL (21–27 days) was associated with lower ORT values as compared to normal (28–31 days), long (32–35 days) and all other (28–35 days) MCL sets. The estimated weighted mean difference (WMD) of AMH level was −1.3 ng/mL (95% CI: −1.75 to −0.86, P<0.001) between the short and normal MCL sets. The estimated WMD of AFC values was −5.17 (95% CI: −5.96 to −4.37, P<0.001) between the short and normal MCL sets.

The weighted overall odds ratio (OR) of fecundability in natural cycles between women with short versus normal MCL sets was statistically significant (overall OR 0.81; 95% CI 0.72–0.91, P<0.001).

In the IVF setting, fewer oocytes were retrieved in short MCL in comparison to normal, long and all other MCL sets, with an estimated WMD of −1.8 oocytes (95% CI: −2.5 to −1.1, P<0.001) in the short versus normal MCL sets. The weighted overall OR of clinical pregnancy rate between women with short versus all other MCL sets was statistically significant (overall OR 0.76; 95% CI: 0.60 to 0.96, P=0.02).

CONCLUSION

MCL in regularly cycling women is closely related to ovarian reserve biomarkers during the reproductive years. A short MCL (21–27 days), as compared to normal (28–31 days), is significantly associated with lower ORT values, reduced fecundability and inferior IVF outcomes, independent of age.

The drop in Serum AMH level found in our meta-analysis far exceeded the expected AMH decline (5% per year in reproductive years) related to the difference in the weighted mean age of the different MCL sets. Most conspicuously, when comparing the weighted mean age of the short versus normal MCL sets, serum AMH value of the short MCL set dropped almost by 8-fold more than anticipated.

Likewise, the drop in AFC values found in our meta-analysis far exceeded the highest expected annual AFC reduction correlated to the differences in the weighted mean age of all MCL sets. Most obviously, since the weighted mean age of the short MCL set is only 1 year older than the normal MCL set, the impact of short MCL surpasses the annual decline in AFC value by a substantial margin, equivalent to 11–13 years.

The results imply that short MCL may be a sign of ovarian aging, combining the quantitative and qualitative facets of ovarian reserve. Educational efforts ought to be designed to guide women with short MCL at a young age, who desire children in the future, to seek professional counselling.

REFERENCES