human reproduction   ## LETTER TO THE EDITOR

Increasing number of menstruations in recent generations may contribute to the development of endometriosis: an evolutionary view from a critical analysis of National Health data

Sir,

We read with interest the recent article of the InterLACE Study Team (2019). The great variation in the occurrence and timing of women's reproductive events (age at menarche, first birth, number of children and natural menopause) over 50 years in different populations is of public health relevance and may explain the increasing incidence of hormone-related diseases. In our opinion, the findings emerging from the InterLACE study deserve utmost consideration in the debate regarding the origin of endometriosis.

Endometriosis is a sex steroid-dependent disease with a prevalence nowadays of 5–10% in the general population with an increasing trend in different populations (Giudice and Kao, 2004). Recently, national studies showed that endometriosis is more common in women between their thirties and forties in different countries (Morassutto *et al.*, 2016; Fuldeore and Soliman, 2017) and, certainly, the development and progression of this disease follow local hormonal milieu as oestrogens modulate immune and epigenetic modifications allowing endometrial implants to grow (Bulun *et al.*, 2019). According to epidemiological data, endometriosis presents a different velocity in its progression at different ages and this can be deduced from the fact that (i) the slope of the prevalence curve increases quickly before 30 years of age to flatten out later on and (ii) endometriosis-related symptoms across age groups slope down as the age progresses (Fuldeore and Soliman, 2017). In fact, the incidence of endometriosis in different countries grows quicker in the second decade of life (Templeman *et al.*, 2008; Gylfason *et al.*, 2010; Morassutto *et al.*, 2016; Fuldeore and Soliman, 2017) exactly when fertility reaches its peak as demonstrated in ART studies (Johnson *et al.*, 2012). Interestingly, if we plot the curves of age of incidence of endometriosis and age at first birth for the same country, they overlap with a peak around 30 years of age. To explain the steep increase of the endometriosis incidence slope between 20 and 30 years of age, we suggest that endometriosis follows the fertility potential of women probably for a favourable hormonal milieu (Bulun *et al.*, 2019). Another explanation may be linked to the number of menstruations that 'accumulates' in the personal history in women with a genetic tendency to develop the disease (Bulun *et al.*, 2019). Nowadays, in countries like Italy and USA, the mean age at first pregnancy is nearly 30 years so it is easy to calculate that these women had already about 240 menstruations before beginning their reproductive life. Moreover, an earlier menarche (InterLACE Study Team, 2019) and a decrease in the number of pregnancies per woman over the past decades in developed countries (Gylfason *et al.*, 2010;

InterLACE Study Team, 2019) lead to a proportionally increase of the overall number of menstruations during the reproductive age. A direct risk correlation with endometriosis between an early menarche and a short cycle length was reported (Templeman *et al.*, 2008).

From an evolutionary point of view, if we situate the human fertility cycle (cyclical ovulation and menstruation) in the broader mammalian context, full menstruation is restricted to 78 species of primate, 5 species of bat and 1 rodent. All of the other species either have cyclical ovulation with no menstruation (the lining of the uterus is simply reabsorbed) or ovulation induced by sex or by environmental cues such as water/food availability (oestrus). It is consistent with the epidemiological data in the animal kingdom that endometriosis is only found in these species with full menstruation (humans, chimpanzees, rhesus and cynomolgus monkeys, mandrills and de Brazza's monkeys; it can be induced in baboons and marmosets). Another interesting pattern is that in 'primitive' groups there is an inverse correlation between fertility and duration of lactation, which always results in low exposure of women to menses (either they have several pregnancies but short lactational amenorrhea or they have few pregnancies but long lactational amenorrhea). In both cases, the number of menstruations is reduced. In urban contemporary populations this pattern is completely broken as we have few pregnancies and short lactational amenorrhea. Humans in the advanced industrial societies are 'extremely unusual' and in a situation never before seen in human society in the past centuries. Women in Western countries have three times the number of menstruations than traditional societies (Strassmann, 1996) where, in extreme cases (rural Bangladesh), over 50% of a woman's reproductive lifespan has no ovulations (pregnancy and lactation) compared to 8% in the rich countries. Variations in reproductive indices can impact on the risk of endometriosis that is a non-rare disease that may affect seriously woman's health (chronic pelvic pain, subfertility, dyspareunia, sometimes with bowel and urinary tract involvement) that lead to relevant social and psychological effects.

References

Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, Kohlmeier A, Yin P, Milad M, Wei J. Endometriosis. *Endocr Rev* 2019;**40**:1048–1079.

Fuldeore MJ, Soliman AM. Prevalence and symptomatic burden of diagnosed endometriosis in the United States: national estimates from a cross-sectional survey of 59,411 women. *Gynecol Obstet Invest* 2017;**82**:453–461.

Giudice LC, Kao LC. Endometriosis.*Lancet Lond Engl* 2004;**364**: 1789–1799.

Gylfason JT, Kristjansson KA, Sverrisdottir G, Jonsdottir K, Rafnsson V, Geirsson RT. Pelvic endometriosis diagnosed in an entire nation over 20 years. *Am J Epidemiol* 2010;**172**:237–243.

InterLACE Study Team. Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries. *Hum Reprod* 2019;**34**:881–893.

Johnson J-A, Tough S, SOGC GENETICS COMMITTEE. Delayed child-bearing. *J Obstet Gynaecol Can* 2012;**34**:80–93.

Morassutto C, Monasta L, Ricci G, Barbone F, Ronfani L. Incidence and estimated prevalence of endometriosis and adenomyosis in Northeast Italy: a data linkage study. *PLoS One* 2016;**11**:e0154227.

Strassmann BI. The evolution of endometrial cycles and menstruation. *Q Rev Biol* 1996;**71**:181–220.

Templeman C, Marshall SF, Ursin G, Horn-Ross PL, Clarke CA, Allen M, Deapen D, Ziogas A, Reynolds P, Cress R *et al.* Adenomyosis and endometriosis in the California teachers study. *Fertil Steril* 2008;**90**:415–424.

Marco Scioscia[1,*], Horace Roman[2], Edgardo Somigliana[3,4], Pierre-Yves Robillard[5,6]

[1] *Department of Obstetrics and Gynaecology, Policlinico Hospital, Piazza Cristoforo Colombo 1, 35 031 Abano Terme, Padua, Italy*
[2] *Center of Endometriosis, Clinique Tivoli-Ducos, 33 000 Bordeaux, France*
[3] *Department of Clinical Sciences and Community Health, Università degli Studi di Milano, 20 122 Milan, Italy*
[4] *Obstetrics-Gynecology Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20 122 Milan, Italy*
[5] *Service de Réanimation Néonatale, Centre Hospitalier Universitaire Sud-Réunion, BP 350, 97 448 Saint-Pierre, cedex, France*
[6] *Centre d'Etudes Périnatales Océan Indien Centre Hospitalier Universitaire Sud-Réunion, BP 350, 97 448 Saint-Pierre, cedex, France*

*Correspondence address. Department of Obstetrics and Gynaecology, Policlinico Hospital Piazza Cristoforo Colombo, 1-35 031 Abano Terme (PD), Italy. Tel: +393 498 724 206; E-mail: marcoscioscia@gmail.com

Reply: Increasing number of menstruations in recent generations may contribute to the development of endometriosis: an evolutionary view from a critical analysis of National Health data

Sir,

In their letter, Scoscia *et al.* refer to our recent findings from InterLACE (InterLACE Study Team, 2019) to highlight speculations on the development and progression of endometriosis in relation to changes in hormonal exposure as reflected in population-level data on women. First, they suggest that the tracking of endometriosis with the fertility potential of women can be seen in a coincidence of peaks for the incidence of the disease and the age at first birth, as well as fertility trends in ART studies. Second, they point to trends in women in contemporary urban populations having fewer pregnancies and short lactational amenorrhea leading to an increase in the total number of menses experienced by women across reproductive life compared with, for instance, women in traditional rural/agricultural societies (who have more pregnancies and breastfeed longer).

We would suggest there are number of reasons to apply considerable caution in interpreting our findings and other population data in this context. Trends in endometriosis are difficult to estimate due to changes in definitions, diagnostic criteria and access to diagnosis and treatment that have occurred over time. There is also typically a long lag between onset of symptoms and diagnosis, with the latter requiring surgical confirmation. Estimation of peak fertility requires age-specific hormone data. National birth rates are likely to be a poor proxy because they are affected by numerous social and economic factors. For instance, women's interest in achieving their first birth (including seeking medical advice from health professionals) may lead to increased diagnosis for endometriosis around this time.

Birth rates from assisted reproductive technology (ART) data are also problematic as a proxy as they refer to women who are unable to achieve their pregnancy goals without artificial intervention (after natural options have failed). As endometriosis is one possible cause of infertility, it is again not unexpected that diagnoses of endometriosis and use of ART follow similar trends with age. But neither relates to onset of endometriosis or peak fertility, both of which are likely to occur at much earlier ages.

In a number of countries, endometriosis appears to have gained recognition as a public health priority, including in Australia with a recently announced 'National Action Plan for Endometriosis'. It is also clear, however, that detailed evidence is lacking to elucidate the casual pathways involved in the aetiology of endometriosis. We suggest that for epidemiologic studies to provide such insights, they should include early diagnosis of the disease, longitudinal biomedical data for variations in hormone levels across reproductive life and genetic data.

Conflict of interest

The authors declare no conflict of interest.

References

InterLACE Study Team. Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries. *Hum Reprod* 2019;**34**:881–893. doi: 10.1093/humrep/dez015.

Gita D Mishra[*], Ingrid J. Rowlands, and Annette J. Dobson
School of Public Health, The University of Queensland, Brisbane, Australia

*Correspondence. E-mail: g.mishra@uq.edu.au
Brisbane, Queensland, Australia