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INVITED COMMENTARY

Towards a more biologically informative system of endometriosis classification

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The main finding of the study by Colgrave *et al.*, 2020 is that the histological appearance and lesion morphology of peritoneal endometriotic lesions is largely independent of menstrual cycle-related changes, as observed in the matched endometrium samples of patients undergoing laparoscopy for severe menstrual and non-cyclic pelvic pain. Moreover, the study shows a considerable inter- and intra-patient variability in the morphology of the endometriotic lesions during different phases of the menstrual cycle.

This result challenges the widely accepted notion that the morphology of endometriotic tissue shows a parallel responsiveness to steroid hormones in the same way as that observed in the eutopic endometrium. On the other hand, this finding is not surprising as endometriosis is known to be a heterogeneous disease varying in lesion appearance from peritoneal to cystic and deep infiltrating disease. In addition, on a biochemical and hormonal level, a large variability is encountered in the inflammatory reaction and aromatase activity as well as progesterone resistance found around macroscopically similar endometriosis lesions (Bulun *et al.*, 2015). Furthermore, this heterogeneity is also clinically observed demonstrating variable presentations in pain complaints in patients with similar endometriosis lesions, lacking prognostic value for clinical endpoints such as recurrence or progression of the disease. Moreover, on a therapeutic level a high variability in responsiveness, from pronounced to absent effect, is found when evaluating the effect of medical treatment for endometriosis-associated pain (Vercellini *et al.*, 2018).

Therefore, the heterogeneity in histological appearance of peritoneal endometriosis lesions, as observed in the study by Colgrave *et al.*, may aid in disease stratification as the different sub-types of lesions may represent different phases in disease activity or even different phenotypes of the disease. As suggested by Colgrave *et al.* more research is needed on additional lesion characterisation in order to clarify the meaning of the morphological diversity. Consequently, an integrative approach is needed combining clinical, molecular and biochemical data. This may create a set of markers, based on the different types of endometriosis lesions, which may facilitate individualisation of endometriosis therapy. In surgery, the lesion markers may help in balancing between pursuing completeness of surgery in aiming to decrease recurrence rates and overtreatment by risking organ damage. In hormonal therapy, lesion morphology may contribute in tailoring hormonal treatments. Lesion desidualisation, which was absent in a majority of lesions in the current study, may be used as a measure for progesterone responsiveness. As such, more information is needed about the mechanisms of progesterone resistance in endometriosis: how is it developed and is it possible to reverse the resistance by treatment? *In-vitro* cellular models may help to characterise these changes in progesterone response and factors that may influence its expression.

Finally, although endometriosis is classified as a benign gynaecological disease, it shares key features with cancer, such as resistance to apoptosis and stimulation of angiogenesis. Endometriosis lesions, harbour somatic mutations which may contribute to the associated increased risk of ovarian cancer (Anglesio *et al.*, 2017). On the other hand, these alterations in mutations may be part of the fundamental pathophysiology of endometriosis (Lac *et al.*, 2019). Thus, they may be important in driving the growth and survival of endometriosis and therefore may predict the risk of disease progression.

Altogether, the heterogeneity of endometriosis should be seen not as a limitation in research and care but as an opportunity to develop a more biologically informative system of endometriosis classification based on the histologic and molecular characteristics of the endometriosis lesion.

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Conflict of interest

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