Ectopic endometrium in the human foetus (Müllerianosis) must be interpreted cautiously

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Dear Editor,
We read with great interest the nice observations by Signorile et al. of endometrium-like tissue in foetuses supporting the concept of müllerianosis. (1) The data, however, poorly support the speculative and overstretched conclusions. The title is misleading and the discussion partially incorrect.
In the absence of pictures or data of the endometrium and of the expression of estrogen receptors it is difficult to judge how specific this observation was. We therefore would be interested to have more information about the specificity of these markers and whether these markers were positive in all endometrium tissue. It is surprising not to find the word CA125, or the words 'estrogen receptor' in reference 1 quoted to support the choice of CA125 and of estrogen receptors as markers. Also reference 14 from 1989 deals with adult tissues. The authors describe "organoid structures" of "misplaced endometrium in five different ectopic sites: in the rectovaginal septum, in the proximity of the Douglas pouch, in the mesenchymal tissue close to the posterior wall of the uterus, in the rectal tube at the level of the muscularis propria, and in the wall of the uterus." To be able to judge whether this is not an over-interpretation, we have a series of questions: How many ectopic endometrium sites had definite "organoid structures"? What was the morphologic structure of each organoid lesion? Were they tubular structures? Did any appear to be rudimentary attempts to duplicate a müllerian duct? Were some solid adenomyotic nodules or adenomyosis? Were any in the form of peritoneal pockets? Were the ectopic endometrial lesions composed of glands and stroma, stroma only, or glands only? In which of the five ectopic sites, if any, did the endometrium lesions contain smooth muscle?
The title is misleading where it states that the data "sustain the theory of müllerianosis in the pathogenesis of endometriosis." Assuming that the observation is indeed misplaced endometrial tissue, this would support the pathogenesis of developmentally misplaced müllerian tissue - müllerianosis. However, we question the relationship of the pathogenesis of müllerianosis to the pathogenesis of endometriosis since müllerianosis was clearly described as an entity separate and distinct from endometriosis. (2) Endometriosis is an acquired disease whereas müllerianosis is congenital. We do not see how the authors' observations contribute to the different hypotheses concerning the pathogenesis of endometriosis. The conclusion of the abstract therefore is speculative and not supported by data.
We strongly disagree with the authors' statement expressed in title and text that "endometriosis [is] a disease that predisposes to cancer," since none of the data in this article support any relationship with cancer. To formulate this as a conclusion is scientifically incorrect and socially unacceptable. This title and conclusion might be picked up and quoted in the press creating fear for many women with endometriosis. Indeed, the same authors, citing Varma et al. (3) in a nearly contemporaneous review wrote more cautiously: "However, despite the histological and epidemiological evidence linking endometriosis and ovarian cancer, it is still not clear if endometriosis is a real precursor of ovarian cancer, or whether there is an indirect link involving common environmental, immunological, hormonal or genetic factors." (4). Moreover using gene expression profiling of endometriotic cells, endometrial cells, and neoplastic cells, a recent study provides strong evidence that "endometriosis only very rarely degenerates into cancer." (5).
In the discussion section of their paper, the authors called for specific research. Examination of Table 1 reveals that the four fetuses with evidence of ectopic endometrium were 25 weeks gestation or less. Only two fetuses of 16 and 18 weeks respectively– both voluntarily aborted – had the potential to survive as newborn females. Had they survived, there is no evidence that the ectopic endometrial tissue would have persisted beyond birth or menarche. Unfortunately, it is impossible to trace the chain-of-evidence of müllerianosis from fetal development to adolescence and maturity in the same female. However, the authors might continue their investigations at all stages of fetal growth and at autopsies of female adolescents and young adults. The authors are to be commended for their careful dissection of the reproductive organs in human fetuses.

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Competing interests

No competing interests for any of the authors

Answer to comments of prof. Koninckx

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Dear Editor,
We are very happy that our work is raising great interest in the scientific community (see for example Faculty of 1000 Medicine: evaluations for Signorile PG et al J Exp Clin Cancer Res 2009 28 :49

We thank dr. Koninckx and colleagues for their comments on our paper supporting the embryological origin of endometriosis (1). Indeed, we have really appreciated some of the comments that will help us in our future investigations. Nevertheless, we strongly disagree with some of the claims of our colleagues. We will try to follow point-by-point their letter in order to clarify the issues raised.
The colleagues complain the absence of pictures or data of the endometrium. It is surprisingly that the colleagues did not notice that in three out of four of the histological figures we showed in the paper, the endometrium is clearly visible and expressing the same morphological and immunohistochemical pattern of the ectopic endometrium. We can agree with the colleagues that the choice of references to justify the use of oestrogen receptor and CA125 in the manuscript was not completely appropriate; nevertheless, ERalpha is known to be expressed in luminal epithelium of the endometrium and sub-epithelial stroma during the foetal life (2), while CA125 is well established marker of the gynecological tract also during the foetal life (3). Indeed, all the other information they ask about the morphology of the ectopic endometrium, are easily deducible from the histological pictures and from the description in the text, such as the fact that there is a case of adenomyosis, that all the lesions have tubular structure, that smooth muscle cells were not present in the lesions, etc.
The colleagues claim that mullerianosis has been clearly described as an entity separate and distinct from endometriosis (4). We know very well the interesting paper on mullerianosis by Batt and coll. Indeed, in this manuscript, the author speculate with brilliant arguments, based on the assumption that endometriosis is an acquired disease caused by retrograde menstruation, that mullerianosis is different from endometriosis. Unfortunately, they do not scientifically demonstrate this hypothesis, that is in contrast with several anatomo-clinical characteristics of the disease (see discussion of our manuscript). Indeed, in a recent and reliable review it is stated that, though there are several theories, research scientists remain unsure as to the definitive cause of endometriosis (5). In the same review it is clearly stated that proponents of Sampson's theory have never been able to demonstrate in vivo the attachment of menstrual endometrium to peritoneal surfaces and the consequently proliferation and invasion. Consequently, the assumption "Endometriosis is an acquired disease whereas mullerianosis is congenital" is only an hypothesis and it has never been demonstrated. On the other hand, our observation that ectopic endometrium is present during the foetal life represents a proof that endometriosis can be caused by little defects during organogenesis, even if, it is not possible to exclude also other pathogenetic mechanisms.
Concerning the question about the relationship between endometriosis and cancer, we have indicated in the title the fact that there exists an epidemiologically proven association between endometriosis and the outbreak of some unrelated malignancy (see for example ref. 6). Indeed, in the text, as acknowledged by the colleagues, we clearly state that there are not definitive evidences that endometriosis itself is a precursor of cancer. We will stress this concept in our future works.
The colleagues question the fact that there is no evidence that the ectopic endometrial tissue would have persisted beyond birth or menarche. Indeed, the histological and immunohistochemical analysis of the eutopic and ectopic endometrium shows a very similar phenotype. This observation argues against the possibility that this ectopic endometrium could "disappear" during the final steps of organogenesis. Nevertheless, the presence of ectopic tissues of several organs (breast, appendix, spleen, thymus, thyroid, salivary glands, etc.) in adults is a quite common event and clearly demonstrate that dislocated tissues during organogenesis do not "disappear".
Finally, we thank our colleagues for the invitation to persevere in the careful dissection of the reproductive organs in human foetuses. Indeed, our research group is intensely working on this topic since a long time and the results of this activity will be soon available to the scientific community.

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