Endometriosis and pregnancy outcome

In this issue, Nirgianakis et al. (1) present a retrospective analysis of the complications of pregnancy after laparoscopic excision of deep infiltrating endometriosis (DIE). Most important is that excision of DIE does not affect the increased risk of placenta previa, gestational hypertension, and intrauterine growth retardation (IUGR) associated with endometriosis. In addition, the risk of a vaginal delivery was not increased in the entire group or in the 26 women with a vaginal excision of endometriosis.

In the Nirgianakis et al. (1) study previous deep endometriosis surgery seems not to significantly affect the probability of cesarean section or the risk of vaginal delivery. The observation that segmental bowel resection was associated with an increased cesarean section rate might be the consequence of a decision by the obstetrician rather than a clinical necessity. It is reassuring to know that it is unlikely that surgery of the bowel, the pouch of Douglas, or the vaginal cuff without affecting the cervix, would complicate a vaginal delivery.

The risk of postpartum bleeding and placental retention is intriguing and has not been reported before. Although not significant in this small series, it could be caused by pelvic nerve damage during deep endometriosis surgery as occurs for bladder and bowel motility. Much larger series will be necessary to confirm this potentially important observation.

This Nirgianakis et al. (1) article confirms the increased incidence of placenta previa, pregnancy hypertension, and intrauterine growth retardation in women with deep endometriosis. The mechanism of this association has been explained as follows. The human pregnancy is characterized by deep placentation, which is an invasive process with the intravascular presence of endometrial cells and physiological changes of the spiral arteries in the junctional zone (JZ). If this mechanism of vascular transformation fails, there is a risk of women becoming hypertensive with small for gestational age (SGA) babies and preeclampsia. A changed uterine contractility and a JZ dysfunction could be the link between endometriosis and adenomyosis which are believed to be associated (2). Focal adenomyotic nodules are more frequent in women with deep endometriosis. Imaging studies found a strong association of cystic ovarian or deep endometriosis with adenomyosis defined as JZ thickening, diffuse adenomyosis, or focal adenomyotic nodules with a prevalence of 80.6 % endometriosis in adenomyosis and 91.1 % of adenomyosis in endometriosis. We do not know whether some phenotypes of endometriosis specifically correlate with the JZ thickening. Also, hereditary, biochemical, and genetic aspects as clonality of adenomyosis are poorly investigated.

The association of endometriosis and adenomyosis with placenta previa, pregnancy hypertension and SGA babies has been discussed in a recent systematic review (3) and meta-analysis (4). The odds ratios (OR) of large cohort studies evaluating the association of endometriosis with preeclampsia (3) were either slightly increased or not significantly different from a control group. The meta-analysis (4) did not reveal an overall significant increase. Unfortunately, as discussed for the epidemiology of endometriosis, these large cohort studies based on hospital discharge records suffer from an uncertain diagnosis of endometriosis and a variable inclusion of subtle endometriosis. The only study looking specifically at women with deep endometriosis found an OR of 4.1 and this increased risk was confirmed in this study by Nirgianakis and colleagues (1). It is surprising that no study evaluated the incidence of preeclampsia in women with cystic ovarian endometriosis or with typical lesions. Similar observations were made for the association of endometriosis and SGA babies. Several larger cohort studies including those evaluating IVF pregnancies did not show an increased risk. However a meta-analysis showed a weak but statistically significant association with an OR of 1.27 (3). Only IVF pregnancies in women with cystic ovarian endometriosis found an increased risk. Also for the risk of premature delivery, antepartum hemorrhage, and placenta previa, similar observations were made with 7 studies showing no association and 12 studies showing a weakly increased risk (3). The meta-analysis found a significant association (4). The two studies that evaluated specifically deep endometriosis, although small, found a strongly increased risk of premature delivery. Diffuse adenomyosis, but not focal adenomyotic nodules, have a higher incidence for SGA babies.

The data thus range from inconclusive to weakly positive. However, they fail to take into account confounding variables such as age of the women, number of pregnancies, and social class. The fact that none of the studies showed an effect in the opposite direction suggests that the effect is small or fails to reach statistical significance because of confounding variables and sampling bias. The larger studies indeed were based either on women with documented minimal or mild endometriosis or on hospital based discharge records, with their bias as discussed before. The few (smaller) studies that evaluated more severe endometriosis such as cystic ovarian or deep endometriosis did find a stronger association as confirmed in the article in this issue (1). We therefore expect that future studies which will evaluate the risk of preeclampsia, SGA babies, preterm delivery, placenta previa, and antepartum hemorrhage in women with endometriosis stratified by severity and type will find an increased risk with increasing severity and/or type of endometriosis. We moreover would not be surprised to find the same increase in women with severe adenomyosis.

Other endometriosis associated complications during pregnancy are not discussed in this article (1). The very high concentrations of estrogens and progestogens in pregnancy will stop growth of most endometriosis lesions and most women with endometriosis associated pain become pain free as expected. Decidualization of endometriosis lesions can cause diagnostic problems during pregnancy with images suggesting a malignancy in cystic ovarian endometriosis and in deep endometriosis (5). Occasionally bowel and bladder perforations by deep endometriosis lesions occur at the end of a seemingly normal pregnancy. Severe life threatening spontaneous intra-peritoneal bleeding during pregnancy is a rare condition related to endometriosis. Other complications

are acute appendicitis, bleeding from cervical endometriosis and polypoid bladder lesions. The mechanisms of these complications were suggested to be due to decidualization and softening of endometriosis lesions (5) or to an abnormal behavior of some endometriosis lesions. That none of these complications were observed in this series, is not surprising considering their low prevalence. Although it is logical to expect that prior surgical excision will reduce this risk, this conclusion cannot yet be make.

This series (1) is small and the deep endometriosis group, defined as histologically confirmed deep endometriosis (and probably as infiltrating deeper than 5 mm under the peritoneum) is heterogeneous. This group indeed varies from smaller peritoneal lesions to larger lesions requiring a bowel resection and/or a vaginal cuff excision with a variable presence of cystic ovarian endometriosis (see Table 1 in Nirgianakis et al. [1]). Also other confounding variables such as the number of previous pregnancies known to affect the risk of pregnancy hypertension could not be taken into account.

The risk of a vaginal delivery seems to not be increased by previous deep endometriosis surgery. This conclusion however needs confirmation by much larger series of deliveries following deep endometriosis surgery stratified by level and length of bowel resection, size of the nodule and vaginal cuff excision.

That pregnancy complications in women with deep endometriosis persist after deep endometriosis excision, suggests that these are not a consequence of endometriosis. This is consistent with the view that endometriosis is the expression of a series of cumulative genetic and epigenetic incidents. Genetic and epigenetic incidents transmitted at birth constitute the hereditary predisposition of endometriosis. Additional incidents are required for endometriosis lesions to develop. This explains the clonal aspect of endometriosis lesions. Whether the original cell is endometrium following retrograde menstruation, possibly neonatally, or stem cells or bone marrow cells is less important. However, retrograde menstruation overloads the peritoneal cavity with iron causing oxidative stress with blood irritating the mesothelial cells in the pouch of Douglas. Both oxidative stress and mesothelial irritation can be viewed as a cause of genetic or epigenetic incidents. This polygenetic and polygenetic pathophysiology is equally applicable to the pathophysiology of adenomyosis.

This inherited set of genetic and epigenetic changes will obviously be present in all cells including the endometrium, the junctional zone, the myometrium and the immune cells. Many of the observed differences associated with endometriosis might thus be a consequence of a common causal factor. These comprise biochemical differences in the endometrium, infertility, immunology and changes in the JZ affecting placentation and physiological changes of the spiral arteries. This might explain the relationship between endometriosis and pregnancy hypertension and SGA babies.

Research on the endometrium, junctional zone, placentation and physiological changes in pregnancy, endometriosis and adenomyosis, and some aspects of immunology and histopathology might turn out to be the search for understanding similar molecular biological disturbances in the cell.

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