Does adenomyosis cause subfertility/impl? Evidence-based analysis

TM D'Hooghe, MD, PhD,
Leuven (Belgium) and Nairobi (Kenya)
ESHRE Campus Course Winter Symposium
Early Pregnancy SIG ESHRE
Milan, Italy, 18-19 December 2008

Adenomyosis: introduction

- **Definition: heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia.**
- **Prevalence: 1% of female patients, more often made in multiparous patients, in their fourth and fifth decade of life.**
- **Symptoms (nonspecific): soft and diffusely enlarged uterus with menorrhagia (40-50%), dysmenorrhoea (10-30%), metrorrhagia (10-12%), dyspareunia, and dyschezia.**

Adenomyosis: introduction

- **DD: dysfunctional uterine bleeding, fibroids and endometriosis (Azziz, 1989).**
- **Infertility less frequent complaint, may be increasing since more women delay their first pregnancy until later in their thirties or forties**
- **The goal of this review paper is to analyze the evidence for the hypothesis that adenomyosis causes infertility, based on current guidelines of evidence-based medicine.**

Evidence based guidelines for causation in medicine

TYPE OF ASSOCIATION

- **Is there evidence from true experiments in humans or animal models?**
- **Is the association strong?**
  RCT> cohort study> case-control study>case reports
- **Clearly defined groups of patients, similar in all important ways other than exposure to the cause?**

Evidence based guidelines for causation in medicine

TYPE OF ASSOCIATION

- **Were causes and clinical outcomes measured in the same way in both groups?**
  =Was the assessment of outcomes either objective or blinded to exposure (cause)?
  CAVEAT: more aggressive search for outcome in group of cases than in group of controls

  Ideal if outcome is assessed by investigator blinded to allocation of patient to case group or to control group

Evidence based guidelines for causation in medicine

TYPE OF ASSOCIATION

- **Was the follow-up of study patients sufficiently long for the outcome to occur?**
- **Was the follow-up complete?**
  Guideline for completeness:
  < 20% patients lost for follow-up.
- **Is the association consistent from study to study?**

Evidence based guidelines for causation in medicine

TEMPORAL RELATIONSHIP

- **Is the temporal relationship appropriate?**
- **Is the temporal sequence of exposure and outcome in the same direction:**
  first putative cause,
  followed by outcome of interest

DOSE-RESPONSE GRADIENT

- **Is there a dose-response gradient?**
  = longer duration/higher magnitude of the cause results in a longer/stronger effect on outcome

Evidence based guidelines for causation in medicine

DOES THE ASSOCIATION MAKE SENSE?

- **Epidemiological sense?**
- **Biological sense?**
- **Other factors that my cause a spurious association?**
- **Results in agreement with our current understanding of the distribution of causes and outcomes in man?**
- **Is the association limited to a single putative cause and a single putative effect? Eg effect of thalidomide on phocomelia**

Evidence based guidelines for causation in medicine

DOES THE ASSOCIATION MAKE SENSE?

- **Is the association specific?**
- **Is the association analogous to a previously proven causal association?**

EFFECT OF REMOVAL/REINTRODUCTION OF CAUSE

- **Is there any positive evidence from a "dechallenge-rechallenge" study?**
  ie: effect on outcome following removal of cause and reintroduction/induction of cause

Literature review

- PubMed: keyword “adenomyosis AND infertility” 13th April 2007
- N = 2137 papers total
- N =910 papers (11years between 13th April 2007-1st January 1997) – all titles read
- N=25 papers selected and read
- Evidence-based guidelines for causation in medicine applied to the content of these selected papers.

Literature review

- PubMed: keyword “adenomyosis AND infertility” 30th November 2008 (published last 2 years)
- N = 261 papers total– all titles read
- N=9 papers selected and read
- Evidence-based guidelines for causation in medicine applied to the content of these selected papers.

Is there evidence from true experiments in humans or animal models that adenomyosis causes infertility?

- No data

Is the association between adenomyosis and infertility strong?

Case-control study:
baboons with spontaneous adenomyosis
(Barrier et al, 2004)

- **3827 necropsy records:**
  37 cases with adenomyosis
  37 controls (normal uterine histology)
  randomly drawn from the database)

Is the association between adenomyosis and infertility strong?

- **Spontaneous adenomyosis strongly associated with spontaneous endometriosis**
  (OR = 31, 95% CI 4-1348).
- **Adenomyosis strongly associated with lifelong infertility (OR =21, 95% CI 3-897).**
- **Adenomyosis without endometriosis also strongly associated with lifelong infertility**
  (OR =20, 95% CI 2-921).

Is the association between adenomyosis and infertility strong?

Case-control study: baboons with spontaneous adenomyosis (Barrier et al, 2004).

- **Strengths: uniform evaluation of all uteri**
- **Shortcomings:**
  -no matching between control and study group
  -adenomyosis missed in the control group
  (uteri not serially sectioned)?
  -Endometriosis missed in control group
  (necropsy, not laparoscopy)?

Is the association between adenomyosis and infertility strong?

Women: no controlled studies

Uncontrolled studies:

-De Souza et al, 1995: adenomyosis (MRI) in 14/26 (54%) of women with infertility, dysmenorrhea and menorrhagia, including 4 women with co-existing endometriosis (4/14 or 29%).

Association between adenomyosis and endometriosis

1. Uncontrolled studies

Variable prevalence of adenomyosis (MRI) in infertile women with endometriosis:

- 79% (Kissler et al, 2006; Kunz et al, 2005)

up to 90% in women younger than 36 years with fertile male partners.

-27% (44/163) (Bazot et al, 2004): other MRI definition...

Association between adenomyosis and endometriosis

2. Case-control study in infertile women with/without endo

Kunz et al, 2005 (MRI):

1. Larger diameter of PJZone in women with endometriosis (n=160, 11.5 +/- 5.3 mm) than in women without endometriosis (n=67, 8.3 +/- 2.6 mm).

2. Larger diameter of PJZone in: women with moderate to severe endometriosis (12.5 +/- 6.4 mm) than women with minimal to mild endometriosis (10.5 +/- 4 mm).

Is the association between adenomyosis and infertility strong?

Conclusion:

- **Baboons: assocation strong, even in the absence of endometriosis**
- **Women:**

association of adenomyosis with endometriosis likely but variable,

association of adenomyosis with infertility not studied

Is there a temporal relationship between the presence of adenomyosis and the development of infertility?

- No data
- Temporal relationship between long-lasting dysmenorrhea and the development of adenomyosis (Kissler et al, 2007)

Temporal relationship between presence of dysmenorrhea and development of endometriosis

- Prevalence adenomyosis (Kissler et al, 2007)
  - 67% (out of N=70 with severe dysmenorrhea+endo)
  - 87% in women with long lasting dysmenorrhea (more than 11 years)
  - 52% in women who developed dysmenorrhea 1 to 10 years before the study.
- ? Is Dysmenorrhea a cause of adenomyosis?

Does the association between adenomyosis and subfertility make epidemiological sense?

- **Yes.**
- **Prevalence of adenomyosis in subfertile patients may be increasing since more women delay their first pregnancy until later in their thirties or forties**

Does the association between adenomyosis and subfertility make biological sense?

- Proposed mechanism 1:
  Immunological dysfunction → abnormal implantation

Ota et al, 1998: activated immune response with changes in both cellular and humoral immunity,

- strong expression of cell surface antigens or adhesion molecules
- increased number of macrophages or immune cells,
- deposition of immunoglobulins and complement compounds
- high frequency of autoantibodies in peripheral blood

Does the association between adenomyosis and subfertility make biological sense?

- Proposed mechanism 2:
  Abnormal uterotubal sperm transport
- Group of Leyendecker
  (Kissler et al, 2007; Leyendecker et al, 2006; Kissler et al, 2006; Kissler et al, 2005; Leyendecker et al, 1998).

Does the association between adenomyosis and subfertility make biological sense?

- Proposed mechanism 2:
  Abnormal uterotubal sperm transport
- Concept:
  both adenomyosis and endometriosis =
  disease of the endometrial-subendometrial unit or archimetra,
  which proliferates following locally increased levels of oestrogen,
  and results in adenomyosis on the uterine level
  and in infiltrative endometriosis on the pelviperitoneal level
- Abnormal uterotubal sperm transport:
  main reason for adenomyosis- and endometriosis-associated subfertility?

Does the association between adenomyosis and subfertility make biological sense?

- Proposed mechanism 2: abnormal uterotubal sperm transport
- HSSG as model for uterotubal sperm transport
- Kissler et al, 2007

Abnormal uterotubal HSSG
(defined as contralateral transport or no tubal transport) :
61.5% (49/80) of infertile women with endometriosis

Subanalysis of 50 patients with endometriosis:
prevalence of abnormal uterotubal HSSG
78% in women with diffuse adenomyosis (11/14)
54% in women with focal adenomyosis (15/28)
37% in women without adenomyosis (3/8)

Is there a dose-response gradient between the degree of adenomyosis and the degree of infertility?

1. Kissler et al, 2007:
Dose-response relationship between
degree of adenomyosis and
degree of abnormal uterotubal transport
as assessed by HSSG (model for uterotubal sperm transport)

2. Kunz et al, 2005:
Dose-response relationship between
degree of adenomyosis (MRI) and
degree of endometriosis

Is the association between adenomyosis and infertility specific?

- No
- Endometriosis is usually confounding variable
- Endometriosis may affect fertility, also in absence of adenomyosis
- Only baboon study (Barrier et al, 2004) suggests a specific independent effect of adenomyosis on subfertility

Does subfertility disappear when adenomyosis is removed?

- Only uncontrolled case series

Excisional surgery:
only 8 case reports (Wang et al, 2006):
Duration of infertility:4-10 years,
Laparoscopy (n=3) or laparotomy (n=5)
Co-existing endometriosis (2/8)
Postop danazol or GnRH analogues (7/8),
Conception within 5-30 months after surgery
Successful livebirth via caesarean section.

Does subfertility disappear when adenomyosis is removed?

Focused ultrasound surgery for symptomatic focal adenomyosis:

1 case report (Rabinovici et al, 2006)

Patient did not receive postoperative hormonal treatment and delivered a healthy child via a normal vaginal delivery.

Does subfertility disappear when adenomyosis is removed?

Medical suppression:

- **GnRH analogues**
  (Hirata et al, 1993; Silva et al, 1994; Lin et al, 2000)
- **Danazol-loaded intrauterine device**
  (Igarashi et al, 2000).

Small series of case reports with successful conception/pregnancy

Conclusion: not sufficient data (all uncontrolled)

Overall conclusion

Preliminary data suggesting an association between adenomyosis and subfertility,

1. case-control study in baboons: strong assocation, even in absence of endo
2. Association makes epidemiological and biological sense
3. Dose-response effect has been observed between degree of adenomyosis, and degree of abnormal uterotubal transport (HSSG model), and degree of endometriosis

Overall conclusion

Quality of evidence is limited to case reports, case series and, at most, case-control studies.

1. Not studied in women:
   strength of association,
   temporal relationship,
   effect of surgery/medical suppression
2. Main problem:
   Association is not specific:
   endometriosis is important confounding variable

Overall conclusion

Needed:
Better designed studies to assess
the prevalence of adenomyosis
in fertile women and infertile women
with and without endometriosis

Important remaining question:
is adenomyosis more than an ultrasound marker for endometriosis?

Acknowledgments

- Leuven University: Endometriosis Research Unit, Division of Reproductive Medicine, Dept OB GYN
  A Mihalyi, PhD; C Kyama, P Simsa, C Meuleman, MD; PR Koninckx, MD, PhD
- Institute of Primate Research, Nairobi, Kenya: J. Mwenda, PhD; D. Chai, DVM; CS Bambra, PhD
- Harvard Medical School, Boston, USA
  (BWH, 93-95: JA Hill, MD; DJ Anderson, PhD)
- Karolinska Institute, Stockholm, Sweden: H. Falconer, MD; Fried, MD
- University of Budapest (Vilmos, MD)
- Ann Arbor University, Michigan, USA (D.Lebovic, MD)

Funding

- Leuven University Research Council: funding since 1998 (2x renewed, up to 2008)
- Belgian Fund for Scientific Research
- Belgian Institute for Science and Technology
- Endometriosis Association
- Serono BENELUX and Corporate Geneva
  Serono Chair in Reproductive Medicine 2005-2010