

How and why to get earlier diagnosis of endometriosis?



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Presentation outline

- Endometriosis in adolescents and young women
- Lengthy diagnostic delays
- Non-invasive diagnosis of endometriosis
- Can earlier diagnosis impact the outcome?
- Implications for clinical practice



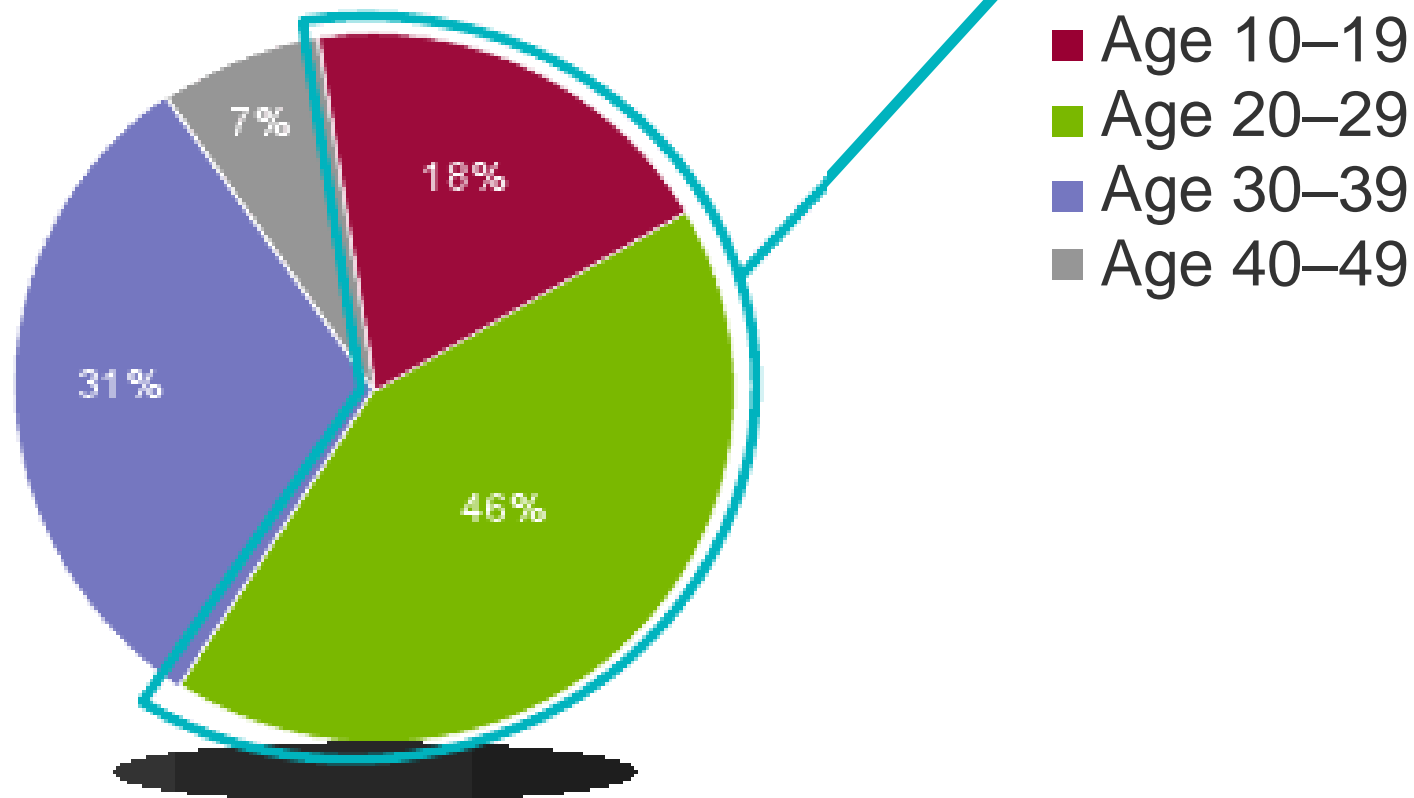
Endometriosis in adolescents and young women

- Endometriosis affects women during the prime years of their lives!
- Women at age ≤ 23 yrs account for $> 20\%$ of endo-related outpatient visits
- ✓ Present in 69% of adolescents with pain refractory to NSAID's or OCP's

Candiani M, et al: J Endometr 2010; 2:24

Age at first consultation for symptoms

64% were <30 years

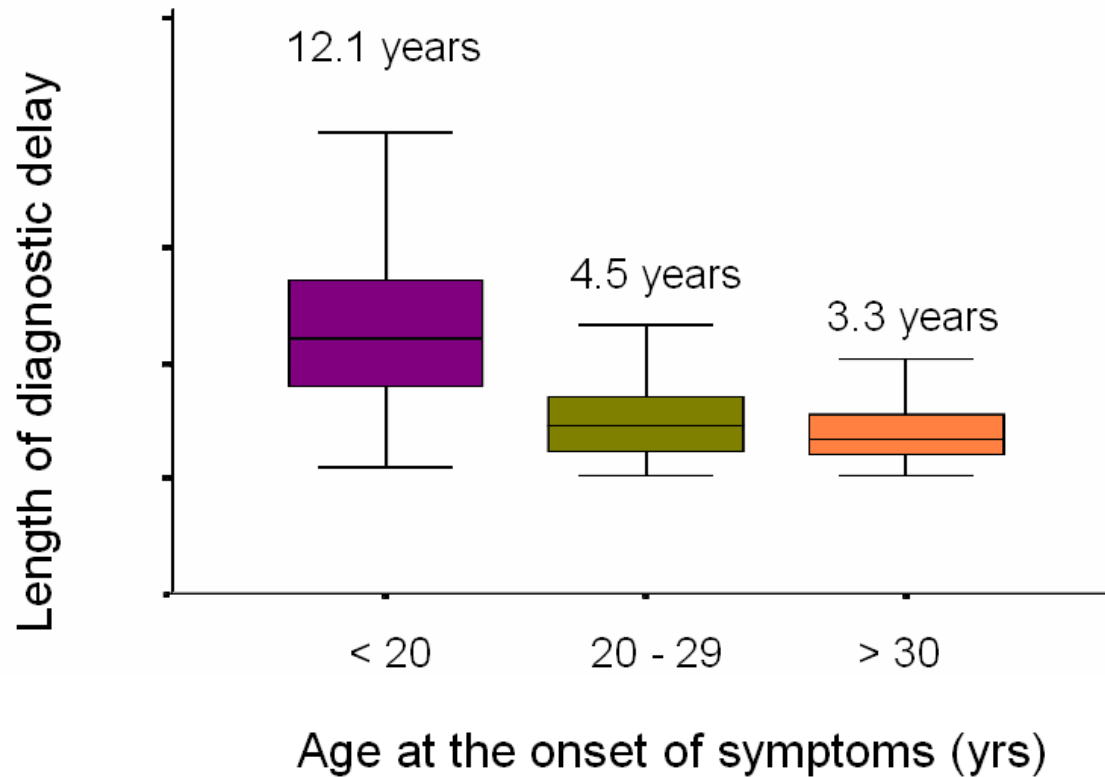


WERF prospective Global Study of Women's Health (n=1,418)

Nnoaham KEL, et al. Fertil Steril 2011;96:366–73

Lengthy diagnostic delays

Mean of 7 years from the onset of symptoms to diagnosis



Lengthy diagnostic delays

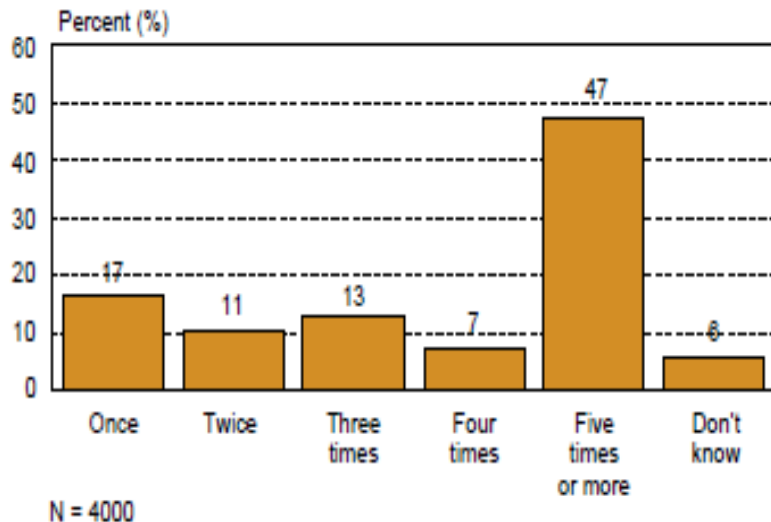


Figure 9. Number of times doctor seen before diagnosis or referral.

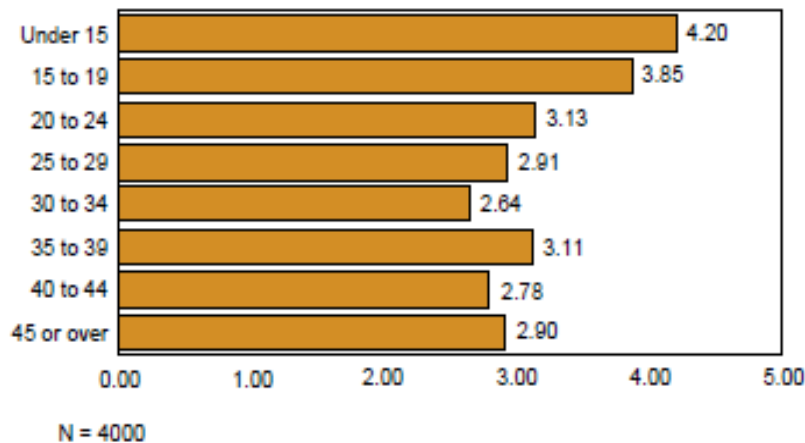


Figure 10. Mean number of doctors seen, by age of first pelvic symptoms.

- %47 had to see ≥ 5 MDs, pre-Dx
- Those with the earliest onset of symptoms had to see more MDs (4.2 if onset <15 yrs old, 2.6 if onset started 30-34)
- delay between onset of symptoms and actual diagnosis = 9.28 yrs
- 4.67 yrs delay to report symptoms to MD, another 4.61 yrs delay to Dx (4.1 yrs gyn ; 1.4 yrs rep.endo ; 5.3 yrs fam. pract)

Biological markers in non-invasive diagnosis of endometriosis

- Surgically diagnosed endometriosis cases in 182 studies
May KE et al. Hum Reprod Update 2011; 17:637–53
 - ✓ high quality - 9 studies
 - ✓ sensitivity & specificity could be calculated - 32 studies
 - ✓ the most promising markers - nerve fibres and molecules involved in cell-cycle control, cell adhesion and angiogenesis
 - ✓ no marker was conclusively shown to be diagnostic

- Se. CA-125 - limited performance in grade I/IV, better in grade III/IV
Mol BW et al. Fertil Steril 1998; 70:1101–08

Immunological biomarkers in non-invasive diagnosis of endometriosis

- Genome wide transcriptional profiling indicated that endometriosis has an immunological basis
Hever A et al. Proc Natl Acad Sci USA 2007;104:12451–6
- ✓ Autoimmune involvement proposed
Mathur S et al. Fertil Steril 1988;50:860–3
Fernandez-Shaw S et al. Hum Reprod 1996;11:1180–4
Randall GW et al. Am J Reprod Immunol 2007;58:374–82
- Among over 200 investigated possible immunological biomarkers, none clearly shown to be of clinical use
- The discovery of biomarkers with high sensitivity, specificity and clinical relevance useful for non-invasive diagnosis is still awaited

ESHRE Endometriosis Guideline Development Group September 2013

Recommendations

Clinicians are recommended not to use biomarkers in endometrial tissue, menstrual or uterine fluids to diagnose endometriosis (May, et al., 2011).

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Clinicians are recommended not to use immunological biomarkers, including CA-125, in plasma, urine or serum to diagnose endometriosis (May, et al., 2010, Mol, et al., 1998).

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Why diagnose early?

Can earlier diagnosis impact the outcome?

- We do know:
 - Persistent pain becomes chronic

- We don't know:
 - Who will develop progressive disease
 - Who will regress
 - Who will stay stable

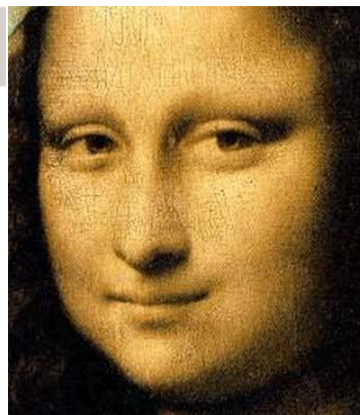
 - Decrease in
 - ✓ Chronic pain risk ?
 - ✓ Infertility risk ?

- To explain the pain
 - Improve validation of symptoms and reduce feelings of isolation

“We can cope with almost anything, if we can understand it”

Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion

I. Brosens^{1,*}, S. Gordts¹, and G. Benagiano²



The presence of endometriosis in the adolescent seems similar to a Mona Lisa smile with a mysterious innocence

Table 1 Staging of endometriosis according to r-AFS classification in adolescents with chronic pelvic pain.

	Nr	Age range	Staging	I (%)	II (%)	III (%)	IV (%)
Goldstein <i>et al.</i> (1980)	66	10–19	K ^a	58	38	0	4
Vercellini <i>et al.</i> (1989)	18	11–19	r-AFS	67	33	0	0
Davies <i>et al.</i> (1993)	36	13–20	r-AFS	28	22	19	31
Reese <i>et al.</i> (1997)	49	11–19	r-AFS	80	12	6	2
Laufer <i>et al.</i> (1997)	32	13–21	r-AFS	77	23	0	0
Emmert <i>et al.</i> (1998)	37	11–19	M ^b	92	8	0	0
Bai <i>et al.</i> (2002)	39	14–21	r-AFS	10	44	28	18
Ventolini <i>et al.</i> (2005)	28	12–18	r-AFS	14	39	43	4
Stavroulis <i>et al.</i> (2006)	11	13–20	r-AFS	45 ^c		55 ^d	
Vicino <i>et al.</i> (2010)	38	15–21	r-AFS	18	13	34	34
Roman (2010)	20	14–20	r-AFS	40	45	5	10
Yang <i>et al.</i> (2012)	63	12–20	r-AFS	8	3	52	37

r-AFS, The American Fertility Society (1985).

^aK based on the criteria of Kistner *et al.* (1977).

^bM based on the endoscopic endometriosis classification (Mettler, 1989)

^cStages I and II.

^dStages III and IV.

↔
%70

↔
%30

A progressive disease ?

- Adolescents' & adults' lesions are similar (subtle, superficial red, vesicular also extensive adhesions and ovarian endometriomas)
Brosens I et al. Hum Reprod, 2013;28:2026–31
- L/S at age 16.6 yrs ; 50% Stage I / II and 50% had Stage III / IV
Davies GD et al. J Adolesc Health 1993;14:362–68
- no difference in stages between adolescents aged 18–19 vs 19+ yrs
- ✓ 75 vs 66% severe endometriosis
Vicino M et al. J Pediatr Adolesc Gynecol 2010;23:223–25
- Adolescent endometriosis is no different from adult endometriosis
Roman JD. Aust N Z J Obstet Gynaecol 2010;50:179–83
Vitonis AF et al. Hum Reprod 2010;25:1325–34
- The behavior is unpredictable, independent of stage, lesion, site, sometimes self-limiting its spread, even regressing.
Vercellini P et al. Hum Reprod 2006; 21:2679

Recurrent endometriosis and repetitive conservative surgery

- In the past two decades the growing popularity and widespread diffusion of operative laparoscopy has fostered a spread of surgical procedures in women with endometriosis
- The behavior of endometriosis is unpredictable regardless of the type of surgical approach.
- ✓ no data are available on reoperation for DIE

Croignani PG et al. Fertil Steril 1996;66:706

Busacca M et al. Am J Obstet Gynecol 1999; 180:519

A progressive disease ?

- Retrospective, 90 cases
- Mean age 17 (12-24)
- Mean stage – I (max. III)
- Ablation/medical Rx
- Intersurgical interval median 29 months (6-112 mths)
- Re-LS indication – symptomatic recurrence

Table 1. Patient Statistics

	Median	Minimum	Maximum
Age (years)	17	12	24
Stage at 1st Surgery	1	1	3
Stage at 2nd Surgery	1	1	3
Stage at 3rd Surgery	1	1	2
Duration between 1st and 2nd Surgeries (months)	29	6	112
Duration between 2nd and 3rd Surgeries (months)	27	9	62
Medical Therapies Used Between 1st and 2nd Surgeries			
		n	%
Continuous combined oral contraceptives		82	91%
Progesterone only		11	12%
Leuprolide acetate +/- addback		70	78%

A progressive disease ?

Table 2. Change in Stage of Endometriosis between Surgeries

	Between 1st and 2nd Surgery	
	n	%
Improved by Two Stages	1	1%
Improved by One Stage	17	19%
Stage Unchanged	63	70%
Worsened by One Stage	9	10%
Total	90	100%
Likelihood of increase (worsening) in disease stage		$P = 0.29$
Likelihood of decrease (improvement) in disease stage *		$P < 0.0001$

	Between 2nd and 3rd Surgery	
	n	%
Improved by Two Stages	1	3%
Improved by One Stage	6	18%
Stage Unchanged	23	70%
Worsened by One Stage	3	9%
Total	33	100%
Likelihood of increase (worsening) in disease stage		$P > 0.99$
Likelihood of decrease (improvement) in disease stage		$P = 0.77$

* especially stages II-III

Recurrent endometriosis and outcome of repetitive conservative surgery

Table 1 Outcome of repetitive conservative surgery for recurrent endometriosis in women with pelvic pain

Author	No. of patients	Surgical approach	Stage III-IV [n (%)]	Months from first surgery	Follow-up (months)	Pre-operative pain [n (%)]	Pain recurrence ^a [n (%)]	Retreatment [n (%)]	Cumulative recurrence (%)
Candiani <i>et al.</i> [4]	42	lpt	39 (93)	48 (8-120)	42 (12-119)	32 (76)	8 (25)	6 (14)	nr
Busacca <i>et al.</i> [5]	41	lpt	39 (95)	47 ± 40	54 ± 30	32 (78) ^b	7 (22)	4 (10)	34 ^b
Busacca <i>et al.</i> [5]	40	lps	32 (80)	60 ± 50	21 ± 10	35 (87) ^b	10 (29)	2 (5)	44 ^b
Fedele <i>et al.</i> [6]	54	lps	54 (100)	nr	35 ± 28	37 (69)	8 (22)	8 (15) ^c	17

lpt, laparotomy; lps, laparoscopy; nr, not reported.

^aPain recurrence rate is calculated only among patients who had pain as main indication for repeat surgery.

^bDysmenorrhoea.

^cMedical or surgical.

- Repeat conservative surgery for pelvic pain associated with recurrent endometriosis has the same limitations as primary surgery, with long-term cumulative recurrence rates ranging from 20-40%, further surgical procedure between 15-20% ^{1 2}
- ✓ Reoperations are technically more challenging and more risky
- ✓ Potential damage to ovarian reserve, morbidity, and the paucity of skilled surgeons ³

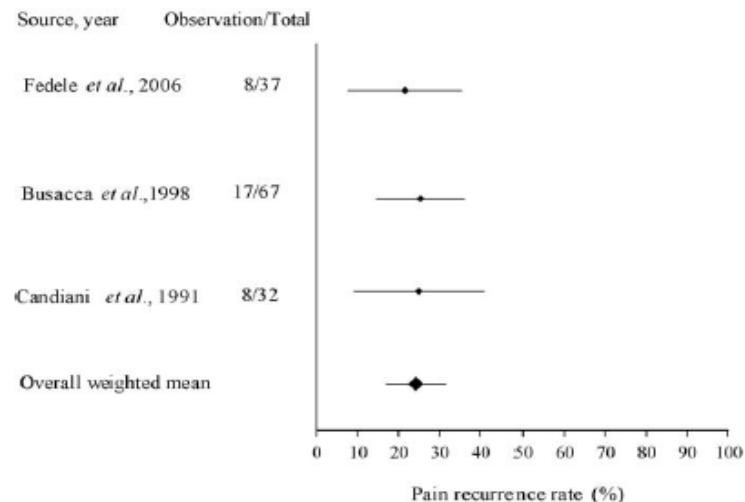


Fig. 1. Pain recurrence rates observed after second-line conservative surgery for endometriosis. Diamonds represent percentage point estimates and horizontal lines 95% C.I.s. Only patients with moderate to severe symptoms before reoperation are included.

¹ Berlanda N. *Curr Opin Obstet Gynec* 2010, 22:320-325

² Vercellini P *et al.* *Europ J Obstet Gynec Repr Biol.* 2009;146:15-21

³ Adamson GD. *Fertil Steril* 2005; 84:1582-84

Recurrent endometriosis

- Younger age at onset or at surgery represent a risk factor for recurrence for both ovarian and deep endometriosis

Liu X et al. Obstet Gynecol 2007; 109:1411

Vignali M et al. J Minim Invasive Gynecol 2005; 12:508

- ✓ ♀ ≤ 21 yrs ; %56 recurrence in 5 years

Tandoi I et al. J Pediatr Adolesc Gynecol 2011; 24 : 376-79

Laparoscopy: advantages and disadvantages

Advantages	Disadvantages ² ³
Gold standard investigation technique ¹	Facilities/surgical expertise not universally available
Possibility to diagnose and treat during one procedure	Not all patients are suitable for invasive techniques
	False-positive and false-negative findings
	Risk of complications

1. Kennedy S, Bergqvist A, Chapron C et al. Hum Reprod 2005;20:2698-2704
2. Brosens IA, Brosens JJ. Eur J Obstet Gynecol Reprod Biol 2000;88:117-119
3. Al-Jefout M, Dezarnaulds G, Cooper M et al. Hum Reprod 2009.24:2972-2973

Surgery alone is not the answer

- There is currently no cure for endometriosis and surgery alone is not an adequate solution
 - Many women (20% to 40%) do not show improvement following conservative surgery ¹
 - Removal of lesions may be incomplete
 - Surgical treatment has risks and, in ovarian endometriosis, is associated with damage to the ovarian reserve ²

“Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures” ³

¹ Leyland N, et al. J Obstet Gynaecol Can 2010;32(7 Suppl 2):S1–S32

² Guo S-W. Hum. Reprod Update 2009;15(4):441–461

³ Practice Committee of ASRM. Fertil Steril 2008; 90:S260

Is surgical diagnosis always necessary

“The common belief that a preliminary laparoscopy must always be performed (**GPP**) in order to definitely diagnose the disease should be challenged, as the non-surgical diagnosis of endometriosis has been demonstrated to be highly reliable”

Guidelines for endometriosis management



Empirical treatment for pain symptoms without a definitive diagnosis *

ASRM=The American Society for Reproductive Medicine;
ESHRE=European Society of Human Reproduction and Embryology;
RCOG=Royal College of Obstetricians and Gynaecologists;
SOGC=Society of Obstetricians and Gynaecologists of Canada.
DoH = Brazilian Department of Health
KSOG – Korean Society of Obstetrics and Gynecology

Streuli, I et al. Expert Opin Pharmacother, 2013;14(3):291-305

Can earlier diagnosis impact the outcome?

- Yes:
 - When
 - ✓ Pathophysiology of the disease
 - ✓ Effective treatment
 - ✓ Non-invasive diagnostic methods
 - are known.

- When we know:
 - Who will develop the disease
 - Who will develop progressive disease

Thereby, when we manage to prevent

- ✓ Symptoms, recurrence.....
- ✓ Chronic pain risk
- ✓ Infertility risk
- **thus improve the quality of life of women**