

PAIN ASSESSMENT IN ENDOMETRIOSIS CLINICAL TRIALS: A REVIEW OF THE LITERATURE

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In the beginning...

1939-1981: PAIN ASSESSMENT METHODOLOGY

- Descriptive
- Analytic

Descriptive Studies

- **Estrogen: Karnaky KJ, South Med J 1948;41:1109**
 - “None with severe dysmenorrhea has been completely relieved of discomfort at menstruation, yet the discomfort is so minimized as to require only one or two aspirin tablets or no medication at all. Most patients wished to continue stilbestrol treatment indefinitely because of the complete freedom from pain...”
- **Estrogen plus progestin: Kistner RW, Fertil Steril 1959;10:539**
 - Case reports, with a narrative of the patients' subjective response and a description of examinations

ANALYTIC STUDIES

- **What was being assessed?**
- **How was the outcome being measured?**

WHAT WAS BEING ASSESSED?

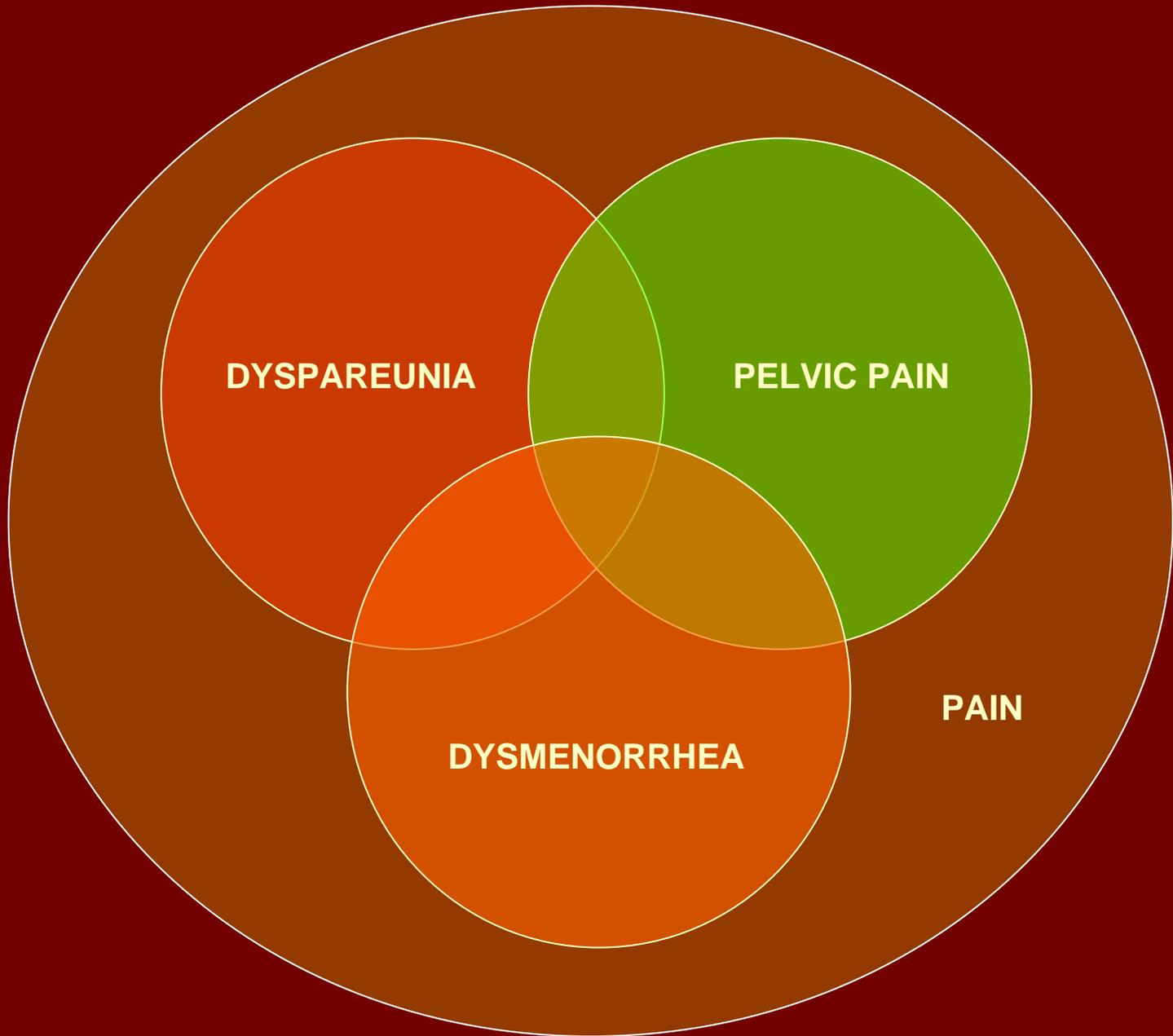
■ Pelvic pain

– Andrews, 1959; Polan, 1980;

■ Subdivision of pain type

– Dysmenorrhea, dyspareunia, pain not related to menstruation, dyschezia, dysuria

- Salmon, 1939; Creadick, 1950; Counseller, 1951; Preston, 1953; Johnston, 1976; Moghissi, 1976; Hammond, 1978;



DYSpareunia

PELVIC PAIN

DYSmenorrhea

PAIN

WHAT WAS BEING ASSESSED?

- Pelvic pain
- Subdivision of pain type
 - Dysmenorrhea, dyspareunia, pain not related to menstruation, dyschezia, dysuria
- Symptoms and signs
 - Pain, uterosacral tenderness, fixed uterus...Andrews, 1959
 - Pain, dysmenorrhea, fixed uterus, adnexal mass/tenderness, nodularity Moghissi, 1976

PROBLEMS WITH CATEGORIES

- Rarely defined
- Unclear if determined by patient or physician

HOW WAS THE OUTCOME BEING MEASURED?

- **Dichotomous global outcome**
 - Relief/no relief...Creadick, 1950
 - Better/not better...Kourides, 1968
- **Graded response**
 - Unchanged, diminished, eliminated...Preston, 1953
 - Not improved, fair, good, excellent...Counseller, 1951
 - Complete, incomplete, failure...Johnson, 1976;
 - 0, 1+, 2+, 3+, 4+...Lauersen, 1975;
 - Occasionally separate category for worsening pain ...Friedlander, 1973

PROBLEMS WITH CATEGORIES

- Demarcations generally undefined
- Unclear if patient or physician assessment
- Reproducibility unclear
- Sensitivity undefined

THE "B&B" SYSTEM

Biberoglu KO, Behrman SJ. Dosage aspects of danazol therapy in endometriosis: short term and long term effectiveness. Am J Obstet Gynecol 1981; 139:645

Endometriosis severity profile scoring system based upon the Biberoglu & Behrman Scale (1981)

Dysmenorrhea	Absent	(0) No discomfort
	Mild	(1) Some loss of work efficiency
	Moderate	(2) In bed part of one day, occasional loss of work
	Severe	(3) In bed one or more days, incapacitation
	Not applicable	(4) Amenorrhea
Dyspareunia	Absent	(0) No difficulty or pain
	Mild	(1) Tolerated discomfort
	Moderate	(2) Intercourse painful to point of interruption of intercourse
	Severe	(3) Avoids intercourse because of pain
	Not applicable	(4) Not sexually active, or prefers not to answer
Pelvic pain	Absent	(0) No discomfort
	Mild	(1) Occasional pelvic discomfort
	Moderate	(2) Noticeable discomfort for most of cycle
	Severe	(3) Requires strong analgesics, persistent during cycle other than during menstruation
	Pelvic tenderness	Absent
Mild		(1) Minimal tenderness on palpation
Moderate		(2) Extensive tenderness on palpation
Severe		(3) Unable to palpate because of tenderness
Induration		Absent
	Mild	(1) Uterus freely mobile, induration in the cul-de-sac, uterine
	Moderate	(2) Thickened and indurated adnexa and cul-de-sac, restricted mobility
	Severe	(3) Nodular adnexa and cul-de-sac, uterus frequently frozen

Administration (daily, monthly or 3-monthly)

- Patient-administered, patient-reported
- Physician/nurse-administered, patient reported
- Physician/nurse-administered, physician/nurse-reported
- Verbal guidance versus script

B&B scores

- ***Separate items:***
dysmenorrhea / pelvic pain / dyspareunia
- ***Sum 3 symptoms:***
dysmenorrhea + pelvic pain + dyspareunia
- ***Sum 3 symptoms + 2 findings (ESS):***
dysmenorrhea + pelvic pain + dyspareunia + tenderness + induration

B&B uses

Typical inclusion criteria

Pain graded at screening using B&B criteria as:

- Moderate or severe pelvic pain not related to menstruation, OR
- Moderate or severe dysmenorrhoea, OR
- Moderate or severe pelvic tenderness on pelvic examination, accompanied by non-menstrual pelvic pain

Typical efficacy measures

Mean changes in pelvic pain scores collected using:

- Daily diaries (dysmenorrhea, pelvic pain + dyspareunia)
- Monthly evaluations (B&B : 3 or 5 items)

% days moderate or severe pain

% improvement in symptom scores

Goserelin -v- danazol. Shaw (1992) *Fertil Steril* 58, 265

Total subjective score : 5 B&B items

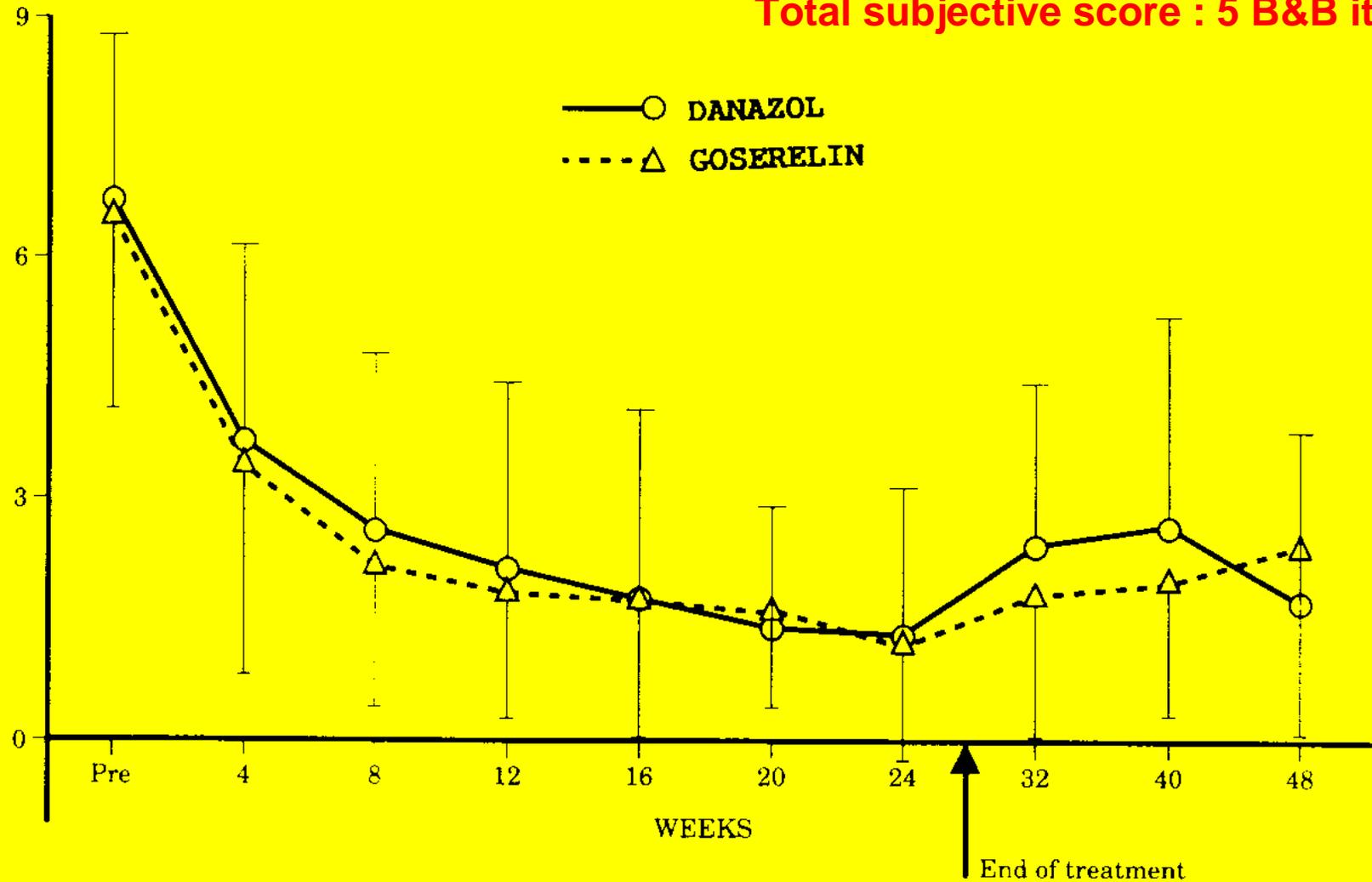
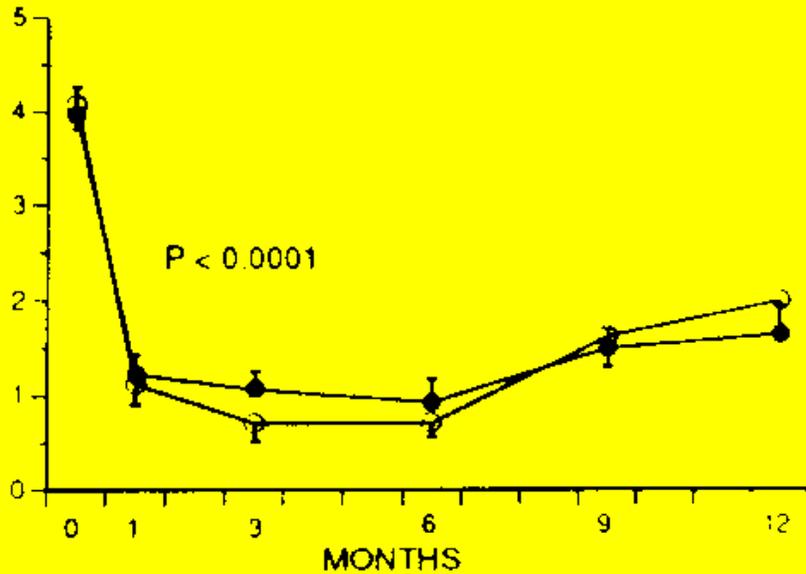


Figure 3 Changes in mean (\pm SD) of total subjective scores (pelvic symptoms and physical findings) during treatment and follow-up in symptomatic patients treated with goserelin (n = 158) or danazol (n = 65).

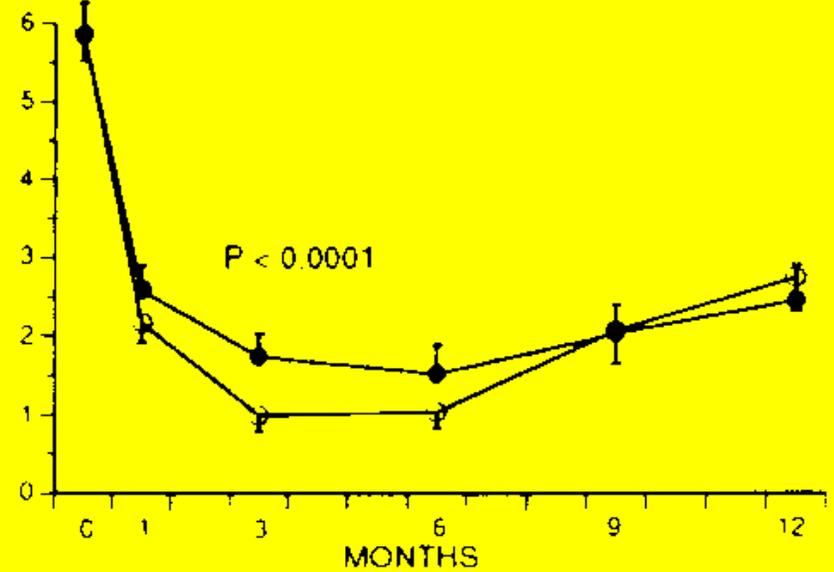
MPA add-back. Makarainen et al (1996) *Fertil Steril* 65, 29

PELVIC SYMPTOMS SCORE



Pelvic symptom score : 3 B&B items

TOTAL SUBJECTIVE SCORE



Total subjective score : 5 B&B items

Nafarelin -v- danazol. NEET Study (1992) *Fertil Steril* 57, 514

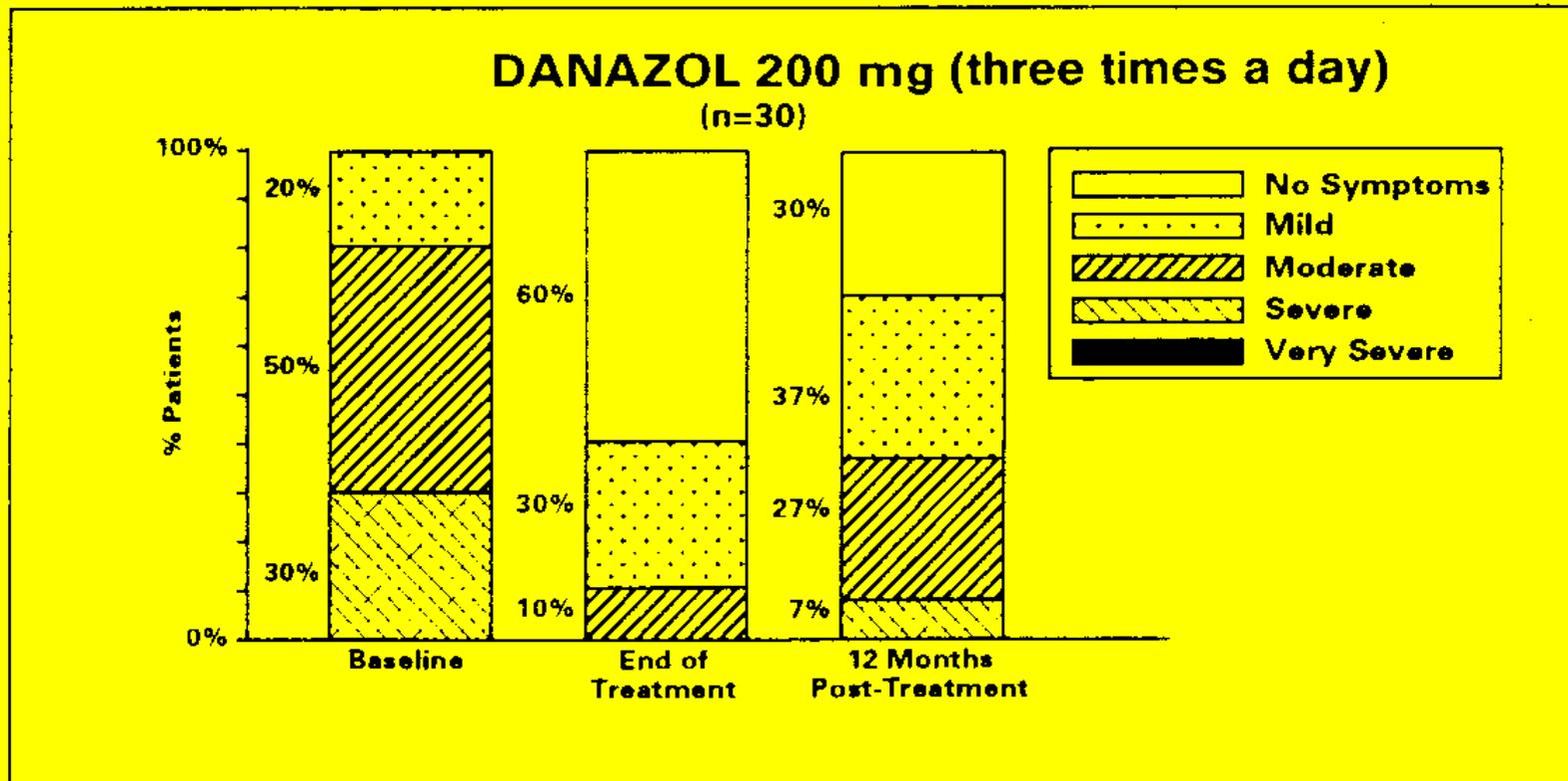


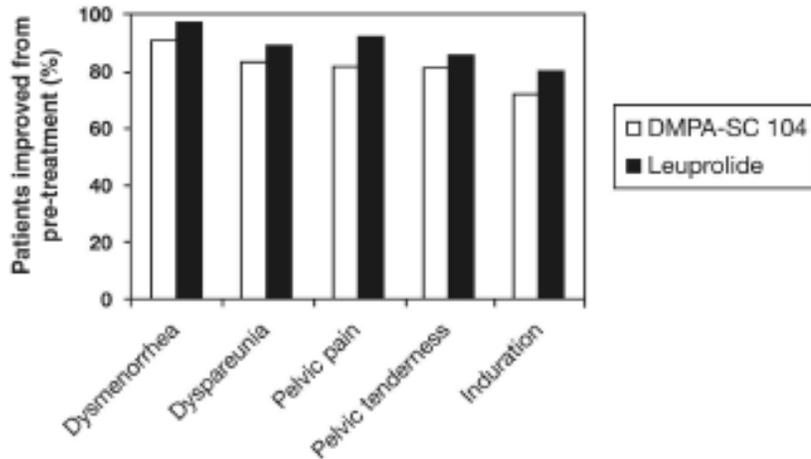
Figure 2 Total symptom severity among patients completing 12-month follow-up. Total symptom severity score is the sum of five separate symptom scores from absent (0) to severe (3) on a four-point scale. The differences from admission and from end of treatment to 12 months post-treatment were significant ($P < 0.001$, McNemar's test) within each treatment group with respect to the proportion of patients improving by at least one severity category.

Total symptom severity score : 5 B&B items

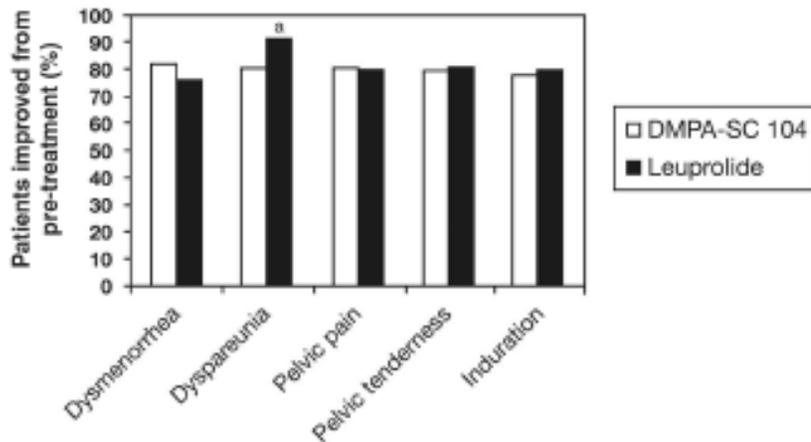
DMPA -v- leuprolide

Crosignani et al (2006) *Hum Reprod* 21, 248

(A)



(B)



Primary efficacy endpoint:

≥1 point improvement at 6 mths

Clinical equivalence to leuprolide:

Improvement in 4/5 'symptoms'

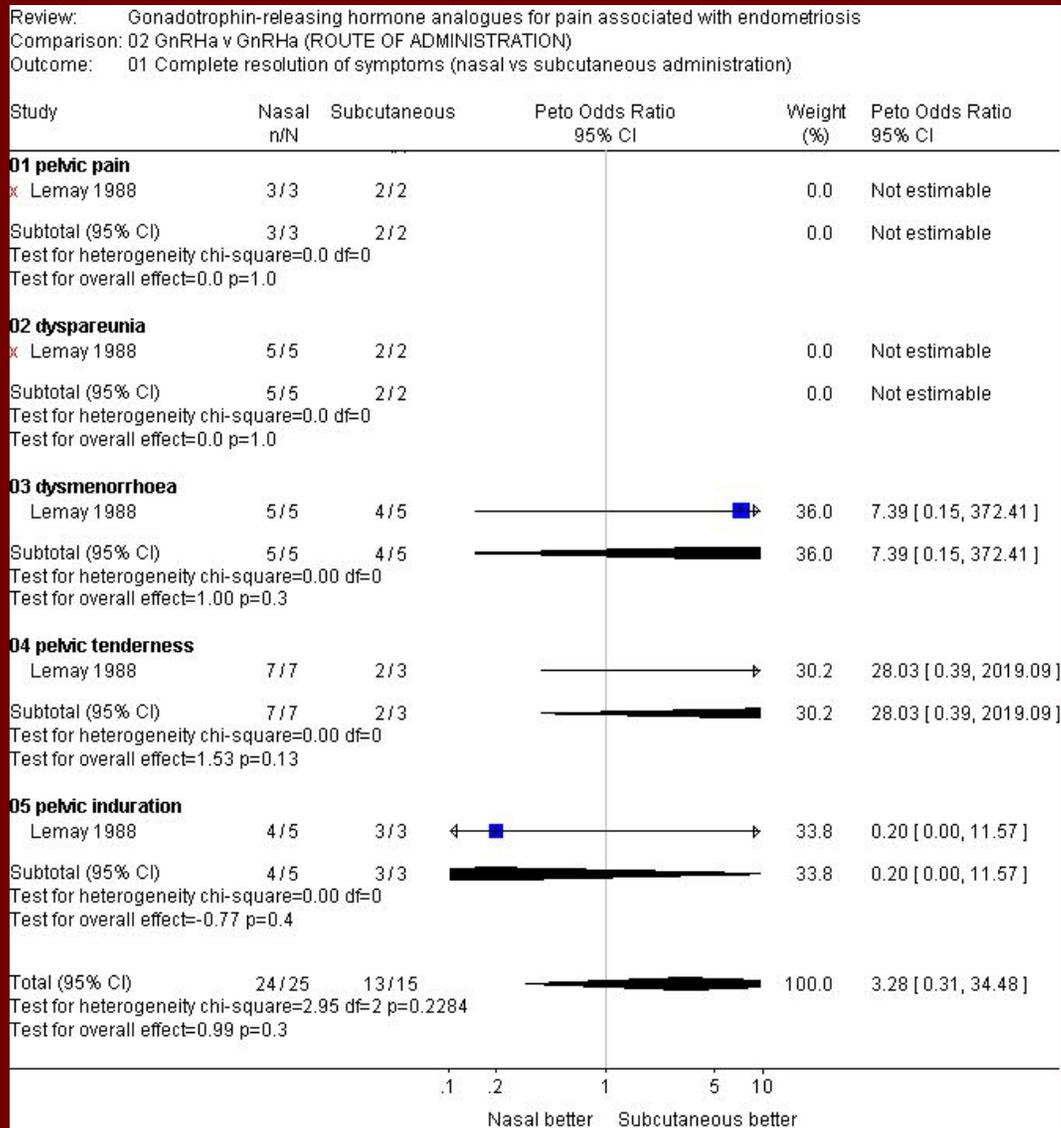
Clinically meaningful improvement:

Mean decrease 4 points in composite score at 6 mths + 12 mths F/U

3 points if not sexually active

(composite score = sum of all 5 individual 'symptom' scores)

Nasal -v- s/c GnRHa. Lemay et al (1988) AJOG 158, 233



Separate scores : 5 B&B items

Principal problems

- Physician derived scales
- Confusion between symptoms and findings
- Pain intensity not measured
- Limited response categories

**IT HAS NOT BEEN SHOWN TO
DEMONSTRATE PRECISION,
REPRODUCIBILITY, OR
VALIDITY**

- Scores added together → large improvement in one symptom may mask deterioration in another (especially if dysmenorrhea major component)
- Lack of consistency → difficulty making comparisons

No pain

Worst possible pain



100 mm scale

VISUAL ANALOG SCALE



Visual analog scale

- Well-validated
- Differences in pain intensity for groups represent actual differences in magnitude, e.g. change from 60 to 30 indicates decrease in intensity and intensity has halved
- High number response categories (10 cm = 101), therefore more sensitive to change than scales with limited number response categories

THE **VAS** IN SURGICAL TRIALS

Sutton et al., Fertil Steril 1994; 62:696

**Randomized comparison of laser ablation and diagnostic laparoscopy
Utilized VAS, global assessment, 10 point patient satisfaction**

Abbott et al, Fertil Steril 2004; 82:878

**Randomized trial of excision and diagnostic laparoscopy
Utilized VAS, global assessment, and 3 QOL measures**

CPA -v- continuous COC after surgery. Vercellini et al (2002) *Fertil Steril* 77, 52



100 mm scale

Mild = 1-50

Moderate = 51-80

Severe = 81-100

Separate VAS's

Dysmenorrhea

Nonmenstrual pelvic pain

Deep dyspareunia

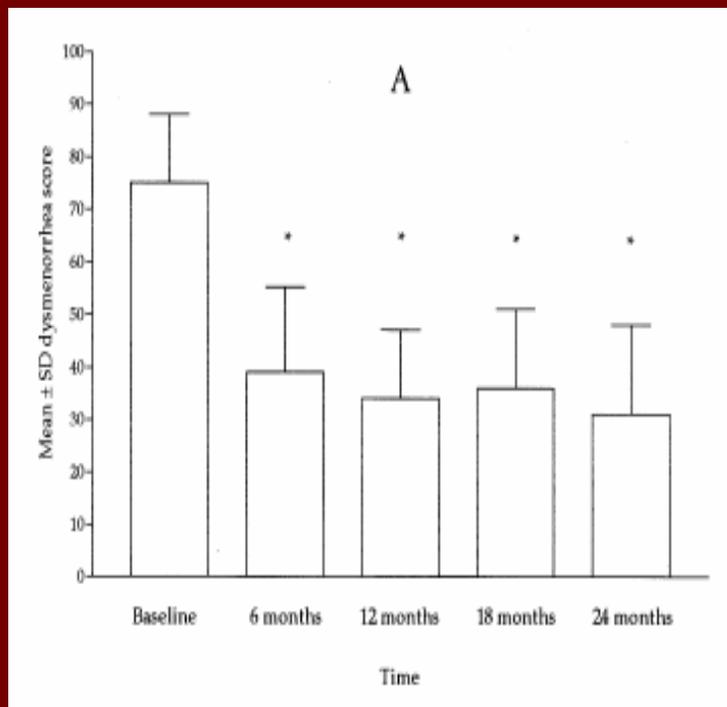
Enrolment criteria

One moderate or severe symptom on VAS + B&B scale

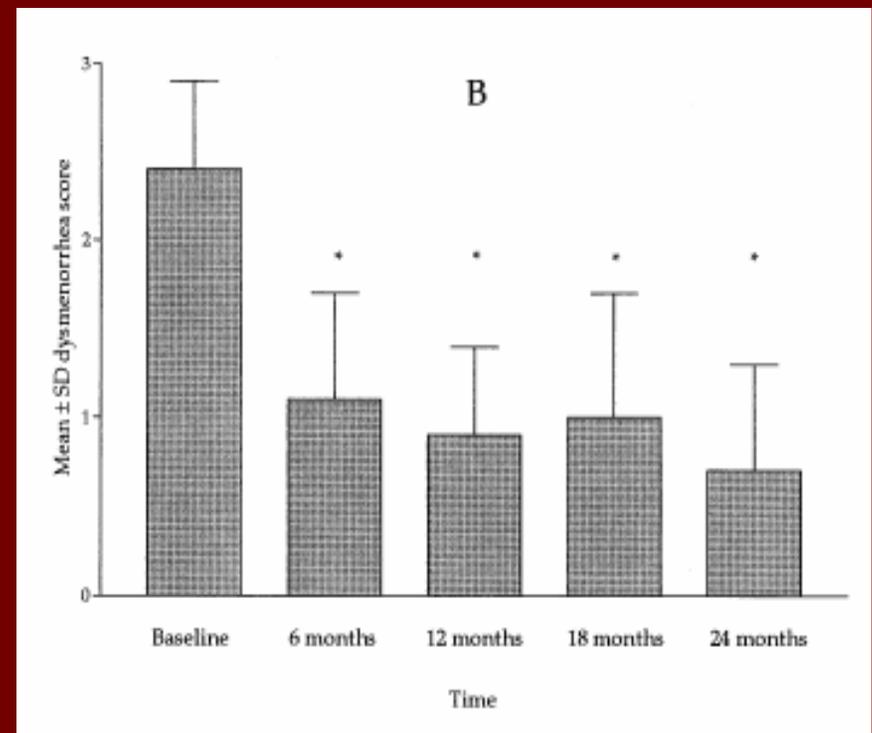
Continuous COC for recurrent dysmenorrhea unresponsive to cyclical COC

Vercellini et al (2003) *Fertil Steril* 80, 560

VAS



VRS



QUALITY OF LIFE

Endometriosis and Quality of Life

- Endometriosis-associated pain has a negative impact on well-being and quality of life¹⁻⁵
 - Affects multiple aspects of a woman's life^{1,4}
 - Affects career, relationships, and feelings of self-worth⁴
 - “Endometriosis demands so much and drains our total well-being”
 - Quote from endometriosis patient⁶

Studies on the Effects of Endometriosis on Quality of Life

Reference	Study Design	Key Findings on Endometriosis
Mathias et al, 1996 ¹	Cross-sectional telephone survey of women: 773 with chronic pelvic pain	Women with diagnoses have increased health distress
Denny et al, 2000 ²	Cross-sectional, qualitative; interviewed 15 patients diagnosed by laparoscopy	Pervades all aspects of life
Cox et al, 2003 ³	Qualitative and quantitative; data from survey and focus groups of 61 women with endometriosis	Described as a disease of losses, affecting career, relationships, and self-worth
Marques et al, 2004 ⁴	Cross-sectional, qualitative; interviewed 60 patients diagnosed surgically	Women with disease have poor quality of life
Lemaire et al, 2004 ⁵	Cross-sectional, descriptive; correlation from written self-report survey from 298 women	Multiple symptoms lead to varying levels of distress

1. Mathias SD et al. *Obstet Gynecol.* 1996;87:321-327; 2. Denny E et al. *J Adv Nurs.* 2004;46:641-648; 3. Cox H et al. *Complement Ther Nurs Midwifery.* 2003;9:62-68; 4. Marques A et al. *J Reprod Med.* 2004;49:115-120; 5. Lemaire GS. *J Obstet Gynecol Neonatal Nurs.* 2004;33:71-79.

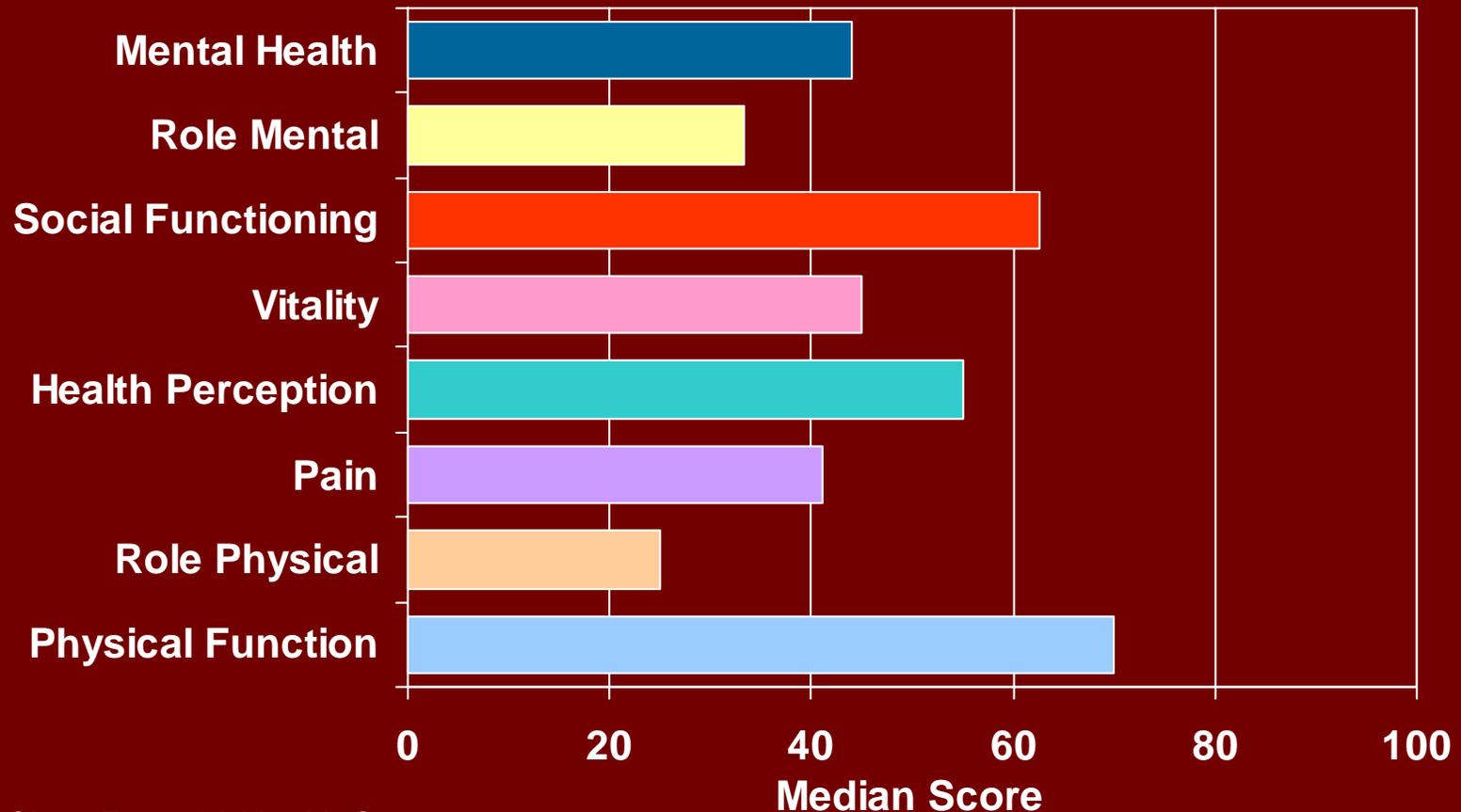
Women's Experiences with Endometriosis

In interviews¹ (n=15) and focus groups² (n=61), women with endometriosis stated these common themes:

- **Difficulties tolerating treatments**
 - **Androgens and GnRH analogs provided only short-term relief, with unpleasant side effects for which women were unprepared¹**
 - **Multiple surgical procedures, often with return of endometriosis^{1,2}**
- **Disruption of work and social relationships^{1,2}**
 - **Illness disbelieved or trivialized**

Women With Endometriosis Have Poor Quality of Life: SF-36 Scores*

N=57 Brazilian women with surgically diagnosed endometriosis



SF-36 = Short Form-36 Health Survey.

*Scores for each scale of the SF-36 range from 0 to 100 (worst to best health status).

Impact of Endometriosis on Health-Related Quality of Life*

- Among 557 women with pelvic pain in the past month:
 - 82% Lacked energy for desired activities at least some of the time
 - 58% Reported 1 or more reduced-activity days in the past month
 - 56% Reported pain interfered with mood at least moderately
 - 47% Reported feeling “downhearted and blue” at least some of the time
 - 26% Reported 1 or more bed days[†] in the past month
 - Mean, 2.6 bed days

*From a telephone survey of 5263 eligible women, N=773 respondents with chronic pelvic pain; [†]Stayed in bed more than half the day.

Distress Associated With Endometriosis

Symptom	Mean Total Symptom Distress Score* (N=298)
Fatigue or weariness	6.24
Menstrual cramping	6.23
Nonperiod pelvic pain	5.41
Lower back pain	5.19
Headache	5.06
Depressed feelings	5.05
Pain with intercourse	4.67
Heavy menstrual flow	4.63
Anxious feelings	4.32

*Scores range from 0 to 9 and represent the sum of symptom frequency, severity, and interference with daily life; higher scores indicate higher distress.

Development of QOL Instruments for Measuring QOL Related to Endometriosis Pain

- Widespread recognition of the severity of this impact has led to the development of disease-specific questionnaires¹⁻⁶
 - Generic questionnaires can be inadequate to assess changes in specific illnesses like endometriosis⁶
 - Complex, multidimensional nature of the disease generated need for disease-specific questionnaires^{5,7}

Quality-of-Life Questionnaires Designed for Endometriosis

- Two questionnaires developed
 - Health-Related Quality of Life (HRQOL)¹
 - Endometriosis Health Profile-30 (EHP-30)²

Quality-of-Life Questionnaires Designed for Endometriosis

- **HRQOL**³
 - First validated quality-of-life questionnaire for endometriosis
 - Multidimensional concept encompassing physical, emotional, and social aspects
 - Contains domains for both global health and domains targeted for endometriosis
- **EHP-30**^{1,2}
 - Questionnaire developed from patient interviews versus existing literature
 - Sensitivity to disease changes demonstrated; useful for assessing impact of interventions
 - Shorter version (EHP-5)³ also developed and validated

OUR CHALLENGE: LEARNING FROM HISTORY

- Develop clear definitions of symptoms (and signs?) of endometriosis
- Develop and utilize valid assessments of endometriosis related symptoms (and signs?)
- Determine characteristics of the instrument(s)
 - Validity
 - Sensitivity
 - Reproducibility
 - Optimal frequency
 - Clinically meaningful change
- Combine with QOL assessments