Review article

Effectiveness of Conservative Surgery and Adjunctive Hormone Suppression Therapy versus Surgery Alone in the Treatment of Symptomatic Endometriosis: A Systematic Review with Meta-analysis.

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Abstract:

Background: Endometriosis is one of the common gynaecological problems mostly affecting the women in reproductive age, associated with non menstrual pelvic pain and other symptoms and recurrence of endometriosis is common after medical or even surgical treatment.

Objectives: This review is done to assess, whether conservative surgery and adjunctive hormone suppression therapy is more beneficiary than surgery alone in the treatment of symptomatic endometriosis in term of pelvic pain and disease recurrence.

Data sources and search method: Searched had been performed on Cochrane Central Register of Controlled trials, MEDLINE, PsycINFO. Journals and reference lists had been also searched.

Review methods: Only Randomized controlled trials were included if they compared the effectiveness of hormone therapy following conservative surgery with surgery alone or surgery plus placebo in the treatment of symptomatic endometriosis. Outcome data had been analysed by using a Mantel-Haenzel Fixed-effect model to perform meta-analysis and results had been presented as Risk ratio for binary data and Standardised Mean difference for continuous data with 95% confidence intervals.

Results: Out of 8 trails pelvic pain was reported in 7 trials. No significant benefit was observed both in pelvic pain recurrence (RR= 0.75, 95% Cl- 0.54 to1.04) and disease recurrence (RR 0.89, 95% Cl 0.53 to 1.49) among 5 trials (481& 447 participants) in favour of surgery and adjunctive hormone therapy. On the other hand another 2 trials (280 participants) showed significant benefit in pelvic pain score (Std. Mean difference-0.80, 95%Cl -1.05 to -0.55) but considerable heterogeneity (I^2= 96%) was observed.

Conclusion: Women who received Post-surgical hormone therapy in the treatment of symptomatic endometriosis had no advantages in respect of endometriosis and pelvic pain recurrence in compared with surgery alone.

Key words: r-AFS (revised American Fertility Society), OCP, RCTs, ASRM (Revised American Society of Reproductive medicine), USG, MeSH (Medical subject heading).

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Introduction:

Endometriosis is a disease characterized by the presence of endometrial tissue outside the uterus[1, 2]. It is a chronic, progressive and second most common gynaecological condition[3] 70% of women with this disease are commonly suffers from chronic pelvic pain[4, 5]. Other symptoms are dysmenorrhoea, dysperunea and infertility[1, 6-8].

The treatment of endometriosis is a problem among even experienced clinicians due to its mysterious characters with a range of treatment option.[9] It is

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known that there is no permanent cure for endometriosis so symptom relief and delaying the disease recurrence by restoring fertility should be the primary goal[7,10, 11]. Conservative surgeries are an effective mode of treatment but recurrence of pain and disease after surgery is very common[7,9,12]. On the other hand hormone therapy acts in endometriosis by arresting menstruation and suppressing normal ovarian function but diseases symptoms reappear soon after cessation of therapy[13].

Theoretically it has been believed that conservative surgery and adjunctive hormone suppression therapy could be better choice of treatment of symptomatic endometriosis in pain reduction and disease recurrence. Hormone suppression may help in complete eradication of any foci of endometriotic tissue which has been escaped after surgery and this can also stops the further implantation and growth of endometriotic tissue disseminated at surgery. But evidence regarding the efficacy of this strategy is necessary to evaluate both benefit and harm before recommending in clinical practice.

Methods:

A systematic review with meta-analysis had been performed including all Randomized Controlled trials (RCTs), where hormone suppression therapy after any kind of conservative Surgery had been compared with surgery alone or surgery plus placebo in the treatment of symptomatic endometriosis.

Search strategy:

Literature had been searched through Cochrane Central Register of Controlled Trials through EBM Reviews up to 1st quarter of 2012, MEDLINE from 1948 to March 2012 and PsycINFO up to March 2012 by using MeSH term and without any language restriction for RCTs. In addition, Human Reproduction Journal, American Journal of obstetrics and gynaecology, Reference lists of included trials and abstracts of review articles had also been searched to identify additional trials to include in this review.

Selection of study:

Only RCTs had been included, where any hormone suppression therapies were used at least for 3 months after conservative surgery. All surgical procedure with restoring normal pelvic anatomy like cystectomy, drainage, excision and ablation were considered for inclusion.

The study participants were considered the women with reproductive age (18 to 49 years of age) with symptomatic endometriosis like stage III-IV [according to r-AFS classification] or Who had an endometriosis scores of ≥4 points according to the (r- AFS) or Stage III-IV [according to the ASRM, 1997 classification] or symptoms of endometriosis with transvaginal-ultrasonographic features of ovarian endometrioma. [14, 15]

Primary outcome of this review were pelvic pain and disease recurrence and secondary outcome were considered as adverse effects like hot flash, headache, hyperandrogenism etc. Studies were included if they measure at least one of the primary outcomes by using any validated rating method.

Trials considering both symptomatic and asymptomatic endometriosis were excluded as sometimes there was no indication to treat asymptomatic endometriosis due to absence of pain and pelvic mass. Moreover the women with asymptomatic endometriosis may differ from the women had symptomatic endometriosis in term of disease characteristics which might introduce bias.

Data abstraction:

Data abstraction was performed by one reviewer on a spreadsheet.

Validity assessment of included trials:

Validity of included trials was assessed by evaluating the five points based on the Cochrane risk of bias assessment tools [16]:

1. Sequence generation; Use of random number table and use of computerized randomization were considered as adequate sequence generation. If study stated just “Patients were randomly allocated” being considered as unclear.

2. Allocation concealment; Centralized allocation using by phone call or using sequentially numbered, opaque and sealed envelopes was considered as adequate. Not mentioning about the method of allocation concealment was assessed as unclear and

3. Blinding; Low Risk of bias considered if the assessment of outcome was blinded unless it was reported that the study was “double blind”.

4. Outcome data; was considered as adequate or low risk of bias if all patients after randomization were included in the analysis of outcome measures. Whilst assessed as high risk if attrition was unequal or more than 20%.

5. Reporting bias; Trials were assessed as low risk of bias if the outcomes of interest were described both in the method and result section.

Statistical analysis:

Analysis was executed by using the RevMan software through Mantel-Haenzel Fixed-effects model to perform meta-analysis. The results were presented as Risk ratio (RR) for binary outcome (pelvic pain and disease recurrence) or Standardised Mean difference for continuous outcome (reduction of pelvic pain score) along with the 95% confidence intervals, (CI). Where RR<1 and Std. mean differ- ence less than '0' was considered as in favour of experimental arm (Surgery plus adjunctive hormone suppression therapy).

Statistical Heterogeneity was assessed by inspecting the I^2 statistic, with values over 50% consistent with substantial heterogeneity. Also observed Chi^2 on n-1 degrees of freedom, where n=number of studies and p-value 0.05 was considered as significant.

Dealing with missing data:

Missing data were not been collected from the original author. Assuming it did not affect the effect size because losses of follow up were less than 10% and almost equal in both arms in most of the studies.

Results:

Search result: Total 17 numbers of references were identified for screening. 6 reports were found as duplicated, 1 study was excluded due to non RCTs, 1 was excluded for using hormone therapy before and after surgery and another 1 was excluded for considering both symptomatic and asymptomatic endometriosis as study participants[17- 19]. Remaining 8 trials (total 1165 participants) were included for analysis.

Methodological quality assessment: (See Table 1)

Effects of intervention:

Among eight trials, six were used 6 months of hormone therapy (GnRH, OCP, Goserelin and Nafarelin) and rest of the two trials used 3 months of hormone therapy (Danazol and Triptorelin) after conservative surgery. Pelvic pain was reported in 7 trials, 5 was reported as binary outcome and 2 measured as continuous outcome and result was expressed in mean± SD. Pain symptom was measured by multidimensional and linear scale in two studies, verbal rating scale in three studies and visual rating scale in two studies[20- 25, 26].

Table 1: Summary of Methodological quality of included 8 trials:

Validity measured	Number of studies (%)
1. Sequence generation	
Adequate	7(88%)
Unclear	1(12%)
2. Allocation concealment	
Adequate	3(38%)
Unclear	5(62%)
3. Blinding	
Not blinded	2(25%)
Unclear	3(38%)
Outcome assessor	2(25%)
Double blinded	1(12%)
4. Outcome data	
Low risk of bias	7(88%)
High risk of bias	1(12%)
5. Free from reporting Bias	
Yes	7(88%)

Table 2: Summary of pooled results (from forest-plot) for primary outcome

Outcome	No of studies	Statistical method	Effect size (95% CI) Subtotal
1. Pain recurrence at different time intervals (Dichotomous)	5	Risk Ratio (M-H fixed effect model)	0.75 (0.54 to1.04)
2. Reduction in pain scores (Continuous outcome)	2	Std. Mean difference (IV, fixed effect)	-0.80 (-1.05 to -0.55)
3. Endometriosis recurrence at different time intervals	5	Risk Ratio (M-H fixed effect model)	0.89 (0.53 to 1.49)

When Meta-analysis was performed for the binary outcome (pain recurrence) among 5 studies at different time interval (Figure 1), pooled result become more precise with narrow Confidence Interval but did not show any statistical significant reduction of pain recurrence (RR= 0.75, 95% Cl- 0.54 to1.04) in favour of experimental arm. Individual trials also did not find any benefit of post surgical hormone therapy compared with surgery alone.

On the other hand Pooled results of pain score (continuous outcome) of other two trials showed statistically significant difference (Std. Mean difference -0.80, 95%Cl -1.05 to -0.55) in favour of surgery plus hormone therapy but considerable Heterogeneity was observed (I^2= 96%, and Chi^2=24.10 with 1 df p<0.00001) (Figure 2). Among these two trials one used dietary fibre with hormone therapy so here dietary fibre could act as an effect modifier and might enhance the effect size[25].

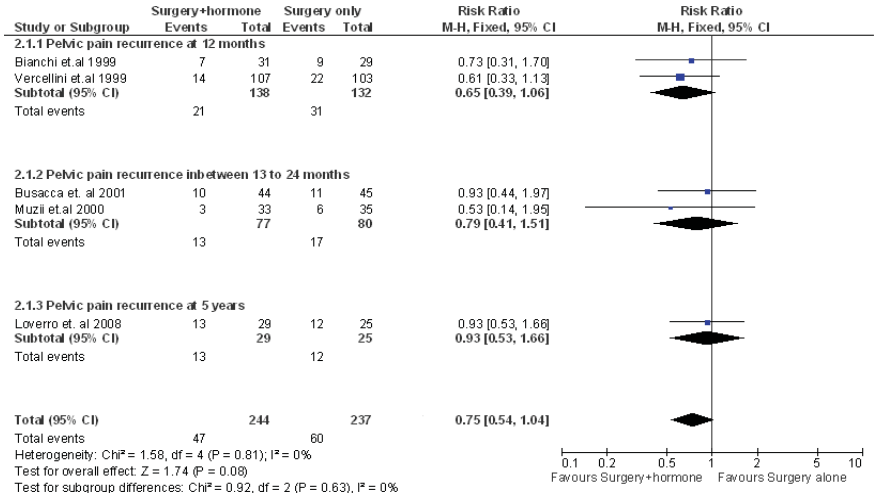

Figure 1: Forest plot: comparison of Surgery and post-surgical hormone therapy versus Surgery alone in pelvic pain recurrence (binary outcome)

Recurrence of Endometriosis was mentioned by 5 trials and pooled result at different time intervals showed no significant differences between experimental and control arm (surgery alone or surgery plus placebo). RR= 0.89, 95% Cl 0.53 to 1.49 (Figure 3). This could be the true result or there might be chance of under estimation of outcome in controlled arm as only one trial used second look by diagnostic laparoscopy after completion of intervention. [7] Other 4 trials used only physical examination and ultrasonography so; there might be chance of missing of any focal lesion of endometrioma or adhesion of disease in final effect measurement.

Adverse effects of hormone therapy were mentioned by 4 trials only but the data presentation did not allow any quantitative analysis[20, 21, 25,27].

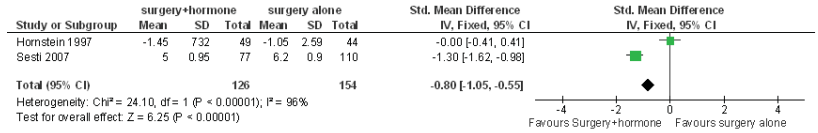

Figure 2: Forest plot: comparison of Surgery and post-surgical hormone therapy versus Surgery alone in reduction of pain score at 12 months (Continuous outcome).

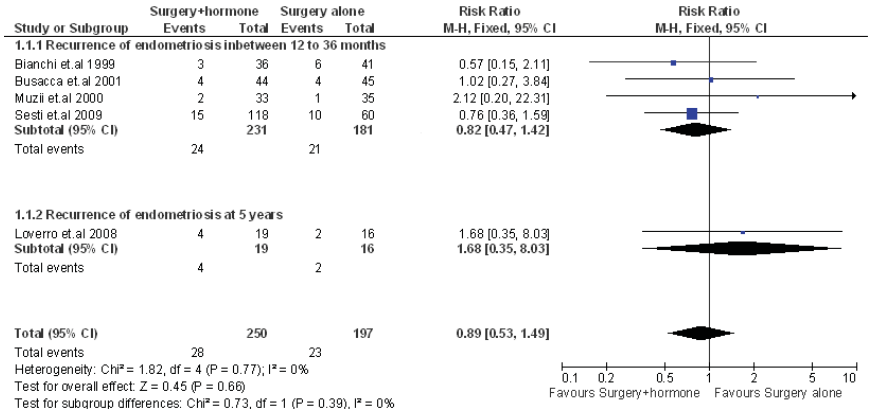

Figure 3: Forest plot: comparison of Surgery and post-surgical hormone therapy versus Surgery alone in disease recurrence (binary outcome)

Discussion:

Very few studies were identified addressing the research question; among those, some studies found statistically significant effect of hormone therapy following conservative surgery in reduction of endometriosis and endometriosis associated pelvic pain symptoms[17,19 ,25].

This review might raise a question why post surgical hormone therapy seemed to be ineffective in comparing with surgery only. The reason could be postulated as: The included trials had very small study population and some were at high risk of bias. The hormone therapy following surgery was also used for shorter duration like 3 or 6 months. The outcome result was expressed in different unit and also measured at different time interval which might be inadequate to quantify the actual benefit of the treatment. The methods of outcome measurement among the studies were also not consistent. Some studies used verbal rating scale, some used visual rating scale and some studies used multidimensional scales. There was also question about methodological quality of the included trials as some studies did not report randomization process adequately as well as allocation concealment.

The research to assess the effect of surgery and post surgical hormone therapy is associated with many complexities. To put sufficient power to the trials recruiting adequate number of participant is difficult because women with sub fertility refuse to take hormone suppression therapy as it reduces or delays their chance of conceiving naturally. Furthermore a very few women agree to undergo for second-look laparoscopy to assess the disease recurrence. Although blinded outcome assessment is desirable in any research, here maintaining blinding is difficult due to the adverse effects of hormone therapy like amenorrhoea which would be obvious to both participant and investigator. But this issue of effectiveness of surgery and adjunctive hormone suppression therapy can be resolved if better designed; sufficiently powered and well conducted trials will be undertaken in future. Consistency in the methods of outcome measure in respect of pain and disease recurrence also reduces the chance of bias. Quantifiable data of adverse events of hormone therapy will help in the assessment of comparative benefit and harms of the experimental arm.

In addition the treatment of endometriosis requires individual evaluation due to its different stages so this combination of treatment can be applied to those experiencing recurrent endometriosis and not desiring to conceive and also experiencing minimum side effects with hormone therapy.

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