International Journal of Gynecology and Obstetrics (2008) **100**, 4–9

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/ijgo

REVIEW ARTICLE

A systematic review of randomized controlled trials to reduce hemorrhage during myomectomy for uterine fibroids ☆

E.J. Kongnyuy [a,*], N. van den Broek [a], C.S. Wiysonge [b]

[a] *Child and Reproductive Health Group, Liverpool School of Tropical Medicine, Liverpool, UK*
[b] *South African Cochrane Centre, South African Medical Research Council, Cape Town, South Africa*

Received 8 May 2007; accepted 13 May 2007

KEYWORDS
Myomectomy;
Hemorrhage;
Tourniquet;
Misoprostol;
Oxytocin;
Vasopressin;
Uterine fibroids

Abstract

Objective: To assess the effectiveness and safety of interventions to reduce blood loss during myomectomy. *Methods:* Electronic searches of the Cochrane Library, MEDLINE, and EMBASE, between 1966 and 2006 for randomized controlled trials (RCTs). *Results:* We found significant reductions in blood loss with vaginal misoprostol (weighted mean difference [WMD] −149.00 mL, 95% confidence interval [CI] −229.24 to −68.76); intramyometrial vasopressin and analogues (WMD −298.72 mL, 95% CI −593.10 to −4.34); intramyometrial bupivacaine plus epinephrine (WMD −68.60 mL, 95% CI −93.69 to −43.51); and pericervical tourniquet (WMD −1870.00 mL, 95% CI −2547.16 to −1192.84). There was no evidence of effect in blood loss with myoma enucleation by morcellation and oxytocin. *Conclusion:* There is limited evidence from a few RCTs that some interventions may reduce bleeding during myomectomy. There is need for adequately powered RCTs to shed more light on the effectiveness, safety, and cost of different interventions to reduce blood loss during myomectomy.

1. Background

The standard treatment of symptomatic leiomyomas (myomas or fibroids) is hysterectomy for women who have completed childbearing and myomectomy for women who wish to preserve fertility. Myomectomy can be accomplished by laparotomy, laparoscopy, or hysteroscopy. Massive blood loss associated with the dissection of huge fibroids renders myomectomy a more technically challenging procedure than hysterectomy. A requirement for transfusion in up to 20% of

☆ This paper is based on a Cochrane Review published in The Cochrane Library 2007, Issue 3 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

* Corresponding author. Liverpool School of Tropical Medicine, L3 5QA, Liverpool, UK. Tel.: +44 151 705 3705; fax: +44 151 705 3329.
E-mail address: kongnyuy@liverpool.ac.uk (E.J. Kongnyuy).

0020-7292/$ - see front matter
doi:10.1016/j.ijgo.2007.05.050

cases following abdominal myomectomy has been reported in the literature, and in 2% of cases there is need for conversion of myomectomy to hysterectomy [1].

A number of interventions have been introduced to reduce bleeding during myomectomy. Three categories of interventions can be identified: (a) interventions on uterine arteries such as laparoscopic uterine artery dissection, uterine artery embolization, pericervical mechanical tourniquet and hormonal tourniquets such as vasopressin and terlipressin; (b) uterotonics such as ergometrine, oxytocin, misoprostol, and sulprostone; and (c) myoma dissection techniques which include the use of laser and chemical dissectors such as sodium-2-mercaptoethanesulfonate (mesna) [2–6].

Despite these procedures excessive hemorrhage during myomectomy remains a major challenge to gynecologic surgeons [1]. The effects of these procedures on blood loss during myomectomy, as reported by previous non-randomized studies, have been inconsistent [3–6]. Moreover, the types of these interventions are so varied that there is need to identify those procedures that are most effective and have the least adverse effects to help the gynecologic surgeon to make a correct choice.

The aim of this review was to assess, using the best available evidence, the effectiveness and safety of interventions to reduce blood loss during myomectomy for uterine fibroids. The use of pre-operative gonadotrophin releasing hormone (GnRH) analogues was not considered in this review because their effectiveness has previously been examined in another review [2].

2. Methods

2.1. Search strategy

Electronic searches were conducted in the Cochrane Menstrual Disorders and Subfertilty Group specialized register, Cochrane Central Register of Controlled Trials (Cochrane Library Issue 1, 2006), MEDLINE (1966 to March 2006), EMBASE (1980 to March 2006), Current Contents (1993 to March 2006), the National Research Register, and the National Library of Medicine's Clinical Trial Register (up to March 2006), by combining search terms for the health condition (myoma*, fibroids, leiomyoma) and the interventions (myomectomy OR laparotomy, laparoscop*, hysteroscop*, uterotonic*, misoprostol, sulprostone, ergometrin*, tourniquet, vasopressin, terlipressin, uterine artery ligation, uterine artery dissection, uterine artery emboli*, mesna, chemical dissection, laser dissection, uterine fibroid emboli*) followed by standardized methodological filters for identifying controlled trials as appropriate [7].

In addition, the above searches were supplemented by contacting experts in the field of myomectomy (for unpublished data) and a hand search of specialist journals, conference abstracts, relevant review articles, and reference lists of identified trials. There were no language restrictions to the search.

2.2. Inclusion criteria

Our inclusion criteria were randomized controlled trials (RCTs) that compared the effect of interventions with placebo or no treatment to reduce blood loss during myomectomy. Study participants were premenopausal women undergoing myomectomy (laparotomy, laparoscopy, or hysteroscopy) for uterine fibroids for any reason. Only interventions performed during surgery, immediately before surgery, or within 24 h prior to surgery were considered for this review.

The primary outcome measures were estimated blood loss in milliliters and need for blood transfusion. Secondary outcomes included duration of operation, intraoperative hysterectomy, conversions from laparoscopy to laparotomy, other intraoperative complications, duration of hospital stay in days, post-operative morbidity, post-operative hemoglobin and hematocrit, abdominal revisions for hemoperitoneum or pelvic hematoma, post-operative recurrence of myomas, pregnancy (if pregnancy desired), treatment adherence, adverse events and cost (total cost, and cost of the intervention).

2.3. Statistical analysis

Data were analyzed using RevMan 4.2 according to standard Cochrane guidelines [3]; analyzing trial participants in groups to which they were randomized, regardless of whether they actually received the treatment assigned. For dichotomous data, we expressed study results as odds ratios (OR) with 95% confidence intervals (CI). We were not able to assess for heterogeneity because of insufficient number of trials in the 7 comparisons (intervention vs placebo/no treatment) considered in this review. Planned subgroup analyses based on the technique of myomectomy (laparotomy, laparoscopy, or hysteroscopy), type of comparison group (placebo or no treatment), and ethnic background (black or white) were not performed for the same reason.

For continuous data, we recorded the means and their standard deviations for each arm of the trial and expressed study results as weighted mean differences (WMD) with 95% CI. Where only the median was reported, we assumed that the mean was equal to the median (after checking for skewness) and estimated the standard deviation from the range (range × 0.95/4). Only one comparison, hormonal tourniquet vs placebo or no treatment, had two trials. There was significant statistical heterogeneity between the study results ($P < 0.00001$, $I^2 = 98.8\%$). Thus, we used the random effects method to pool the data and investigated the source of heterogeneity.

2.4. Description of studies

We identified 17 potentially eligible studies, from which we excluded 4 because further investigation revealed that there was no randomization [3–6], and 5 because the control group was another active intervention rather than a placebo or no treatment [8–12].

The remaining 8 randomized controlled trials with 371 participants met our inclusion criteria: two trials with 58 participants on a hormonal tourniquet, vasopressin [13,14]; one trial on the uterotonic effect of misoprostol [15]; one on oxytocin [16]; one on pericervical tourniquet [17]; one on chemical dissection with mesna [18]; one on the vasoconstrictor effect of bupivacaine plus epinephrine [19]; and one on the enucleation of myoma by morcellation while it is attached to the uterus [20]. We did not identify a randomized controlled trial that assessed the effect of uterine artery ligation or laser dissection of the myoma. In 5 studies, myomectomy was carried out by laparotomy and in 2 studies [19,20] it was by laparoscopy. Both laparotomy and vaginal routes were used in one trial [16].

Further details about the study participants, interventions, type of myomectomy, quality of included studies, and outcomes are presented in Table 1.

3. Results

3.1. Oxytocin

We found no evidence of a difference between oxytocin and placebo in blood loss (1 trial with 94 participants: WMD 57.00 mL, 95% CI −129.22 to 243.22), need for blood transfusion (OR 1.99, 95% CI 0.88–4.54), and duration of surgery (WMD 4.00 min, 95% CI −1.49 to 9.49).

3.2. Misoprostol

Compared to placebo, misoprostol significantly reduced blood loss (1 trial with 25 participants: WMD −149.00 mL, 95% CI −229.24 to −68.76), shortened duration of surgery (WMD −9.50 min, 95% CI −15.90 to −3.10) and increased post-operative hemoglobin (WMD 0.80 g/dL, 95% CI 0.33–1.27). However, there was no evidence of effect on the need for blood transfusion (OR 0.36, 95% CI 0.05–2.50), duration of hospital stay (WMD 0.00 days, 95% CI −0.82 to 0.82), and febrile morbidity (OR 1.25, 95% CI 0.24–6.44).

3.3. Vasopressin and analogues of vasopressin

Compared to participants on placebo, those on vasopressin and analogues had a significant reduction in blood loss (2 trials with 58 participants: WMD [random] −298.72 mL, 95% CI −593.10 to −4.34) (Fig. 1). Though the two trials of vasopressin showed significant reduction in blood loss, there was significant heterogeneity between them ($P<0.00001$, $I^2=98.7\%$), presumably due to use of different types of vasopressin: natural vasopressin (1 trial with 20 participants: WMD −450.00 mL, 95% CI −507.49 to −392.51) and synthetic vasopressin (1 trial with 38 participants: WMD −149.60, 95% CI −178.22 to −120.98). However, we found no evidence that vasopressin has an effect on the need for blood transfusion (1 trial with 20 participants: OR 0.05, 95% CI 0.00–1.03), duration of surgery (1 trial with 38 participants: WMD −28.50 min, 95% CI −61.76 to 4.76), duration of hospital stay (1 trial with 38 participants: WMD 0.55 days, 95% CI −0.10 to 1.20), post-operative adhesions to the bowel/omentum (1 trial with 38 participants: OR 2.02, 95% CI 0.54–7.49), post-operative adnexal adhesions (1 trial with 38 participants: OR 1.87, 95% CI 0.39–8.93), and occurrence of pregnancy one year after myomectomy (1 trial with 38 participants: OR 0.64, 95% CI 0.18–2.31).

3.4. Bupivacaine plus epinephrine

Compared to placebo, bupivacaine plus epinephrine significantly reduced blood loss (1 trial with 60 participants: WMD −68.60 mL, 95% CI −93.69 to −43.51) and duration of surgery (WMD −30.50 min, 95% CI −37.68 to −23.32). No patient required blood transfusion.

Table 1 Characteristics of trials included in the review

Study	Sample size	Interventions	Type of operation	Outcomes
Agostini [16]	94	15 IU oxytocin IV infusion vs physiological serum	Laparotomy or vaginal route	Pre-operative blood loss, blood transfusion, and duration of surgery.
Assaf [13]	38	Intramyometrial injection of ornipressin (5 IU) vs no treatment	Laparotomy	Pre-operative blood loss, operation time, hospital stay, adhesions and pregnancy outcome
Benassi [18]	58	Sodium-2-mercaptoethanesulfonate (mesna) for chemical dissection of myoma vs saline for dissection of myomas.	Laparotomy	Post-operative hemoglobin and hematocrit, duration of operation, hospital stay, and post-operative complications.
Celik [15]	25	400 μg misoprostol vaginally 1 h before surgery vs identical placebo.	Laparotomy	Pre-operative blood loss, post-operative hemoglobin, operation time, blood transfusion, hospital stay, and post-operative morbidity.
Frederick [14]	20	Injection into the broad ligaments of vasopressin during surgery vs injection of placebo	Laparotomy	Pre-operative blood loss and blood transfusion.
Sinha [20]	48	Enucleation of myoma by morcellation while still attached to uterus vs conventional technique of complete enucleation followed by morcellation.	Laparoscopy	Pre-operative blood loss, hospital stay, and length of surgery.
Taylor [17]	28	Pericervical tourniquet vs no treatment	Laparotomy	Pre-operative blood loss, need for blood transfusion, operative morbidity.
Zullo [19]	60	50 mL of bupivacaine cloridrate 0.25% + 0.5 mL of epinephrine infiltrated into myometrium around the myoma before incision vs infiltration of normal saline	Laparoscopy	Pre-operative blood loss and operation time.

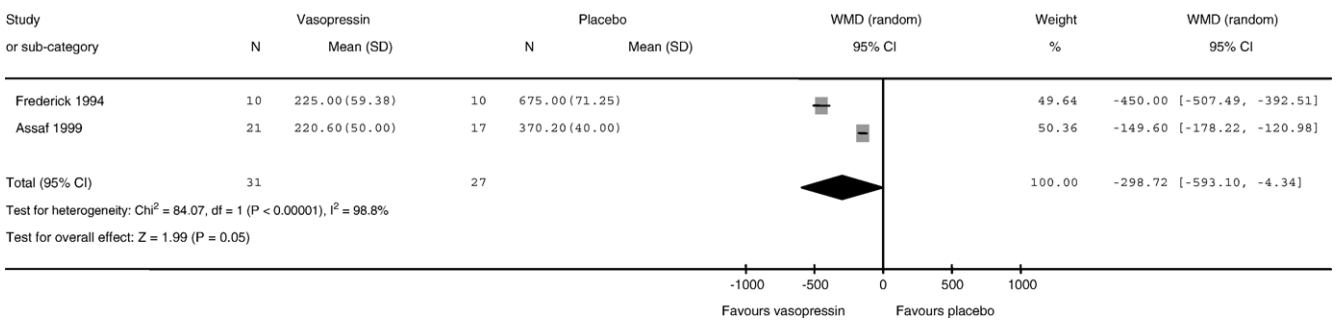

Figure 1 Comparison of blood loss (mL): vasopressin and analogues vs placebo or no treatment.

3.5. Mesna (sodium-2-mercaptoethanesulfonate)

Chemical dissection with mesna significantly reduced the duration of surgery (1 trial with 58 participants: WMD −20.00 min, 95% CI −28.60 to −11.36) and hospital stay (WMD −1.00 day, 95% CI −1.12 to −0.88). Post-operative hemoglobin (WMD 0.50 g/dL, 95% CI 0.42–0.58) and hematocrit (WMD 1.90 g/dL, 95% CI 1.30–2.50) were also significantly increased with mesna compared to placebo, but there was no evidence of effect on the incidence of post-operative fever (OR 0.14, 95% CI 0.02–1.22).

3.6. Pericervical tourniquet

Occlusion of the uterine and ovarian arteries significantly reduced blood loss (1 trial with 28 participants: WMD −1870.00 mL, 95% CI −2547.16 to −1192.84) and the need for blood transfusion (OR 0.02, 95% CI 0.00–0.23). However, the procedure had no evidence of effect on the operating time (WMD −4.00 min, 95% CI −29.28 to 21.28).

3.7. Myoma enucleation by morcellation

Myoma enucleation by morcellation during laparoscopic myomectomy reduced the operating time (1 trial with 48 participants: WMD −25.30 min, 95% CI −44.23 to −6.37), but there was no evidence of effect on blood loss (WMD 65.40 mL, 95% CI −36.47 to 167.27) and duration of hospital stay (WMD −0.07 days, 95% CI −0.18 to 0.04).

4. Discussion

This review evaluated the effect of different interventions on blood loss during myomectomy for uterine fibroids. We identified 8 well designed randomized trials that have assessed the effect of each intervention on blood loss. All the trials had a small sample size.

Some of the interventions showed promising effects on reducing blood loss during myomectomy. Significant reduction of intraoperative blood loss (298.72 mL) was noted when vasopressin is injected into the uterine muscles overlying the myoma during myomectomy. Inspection of the data shows that the WMD was less than zero in each of the two studies that assessed the effect of vasopressin on blood loss; however, the confidence intervals did not overlap suggesting highly significant heterogeneity ($P<0.00001$, $I^2=98.8\%$). Thus despite considerable heterogeneity, we believe that the conclusion that blood loss was significantly lower with vasopressin vs placebo is valid. However, more trials are needed to quantify the actual estimate of benefit from vasopressin. Heterogeneity was thought to be due to the differences in blinding of outcome assessors and the fact that one study used natural vasopressin, while the other study used ornithine vasopressin (ornipressin), a synthetic analogue of vasopressin in which ornithine is found in position 8 of the cyclic nanopeptide.

The injection of bupivacaine plus epinephrine into the myometrium overlying the myoma was evaluated in one study and the result showed evidence of reduction in blood loss, although this might not be useful clinically (68.6 mL). Vasopressin and bupivacaine plus epinephrine are known local vasoconstrictors and may reduce local blood flow when injected around the myoma. The study on the effect of chemical dissection of the myoma with mesna did not directly evaluate blood loss, but showed a significant gain in post-operative hemoglobin. Mesna is a lytic agent that can disrupt connections between tissue layers [21] and may thus facilitate myoma enucleation.

The largest effect on blood loss during myomectomy was recorded by the study that combined the occlusion of the uterine arteries and ovarian arteries using tourniquets prior to myoma enucleation. The uterus receives blood supply primarily from the uterine artery and secondarily from the ovarian artery. Misoprostol, a prostaglandin E2 analogue, was equally shown to significantly reduce blood loss, probably by causing uterine contraction and reducing uterine blood flow.

Other interventions have not been able to demonstrate the expected effect on blood loss that was theoretically postulated. The trial on oxytocin, a known uterotonic agent, showed no evidence of effect on blood loss during myomectomy. This is consistent with other evidence that the myometrial concentration of oxytocin receptors is very low in non-pregnant uteri [22]. Similarly, myoma enucleation by morcellation showed no evidence of reducing blood loss during myomectomy. This could partly be due to the small sample size of these studies.

One way of evaluating difficulty encountered during myomectomy was by measuring operation time. The trials on misoprostol, bupivacaine plus epinephrine, mesna, and myoma enucleation by morcellation all recorded a significant reduction in operation time. The use of oxytocin, pericervical tourniquet, and vasopressin showed no evidence of effect on duration of surgery.

Post-operative outcome was assessed by duration of hospitalization. Four trials included the duration of hospital

stay in their evaluation. Only the trial on mesna recorded a significant decrease in the duration of hospital stay.

There is insufficient data on the adverse effects and costs of different interventions. Trials that commented on adverse effects simply stated that no adverse effects were noted in their trial. Knowledge of adverse events and tolerability of an intervention is important because we have to be able to balance the estimated benefits, and the harms and costs before making any appropriate decisions about use or non-use of the intervention. Evidence from clinical practice has shown that mesna is well tolerated and can be taken orally [23].

In developed countries GnRH analogues have been used prior to myomectomy. There is now clear evidence that the use of GnRH analogues reduces uterine volume and fibroid size and may reduce blood loss and operating time during myomectomy [2]. Although the use of pre-operative GnRH analogues leads to less frequent vertical incisions in the case of myomectomy, a review of the cost-effectiveness of GnRH analogues found that the costs outweigh its benefits [24]. In addition, uterine artery embolization (UAE) has been used as an alternative to myomectomy [25] or to prevent hemorrhage during myomectomy [5]. However, there are currently no randomized trials on the effect of UAE on blood loss during myomectomy. In low and middle income countries, the cost of using GnRH analogues and UAE may be prohibitive (especially where there is out-of-pocket payment) and the necessary technology may not be available.

5. Conclusions

At the moment, there is limited evidence from only a few randomized controlled trials that the use of misoprostol, vasopressin, bupivacaine plus epinephrine, pericervical tourniquet, and chemical dissection with mesna may reduce blood loss during myomectomy. However, since we did not include trials with head-to-head comparison, we cannot draw any conclusion about the superiority of one intervention over the other. At present, there is no evidence that oxytocin and myoma enucleation by morcellation have an effect on intraoperative blood loss.

There is need for more well-designed randomized controlled trials to shed more light on the effectiveness of different interventions to reduce blood loss during myomectomy. Apart from the effectiveness, data on the cost-effectiveness, pregnancy (if desired) and adverse effects of different interventions need to be documented. This is important for clinical decision-making since such decisions should be based on the trade off between benefits on the one hand and costs and adverse events on the other.

Acknowledgments

We wish to thank the Cochrane Collaboration for helping in the development of the protocol and in realization of the final version of this review.

References

[1] LaMote AI, Lalwani S, Diamond MP. Morbidity associated with abdominal myomectomy. Obstet Gynecol 1993;82:897–900.

[2] Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids (Cochrane Review). The Cochrane Review, Issue 2, 2004. UK: John Wiley & Sons Ltd: Chichester.

[3] Liu W, Tzeng C, Yi-Jen C, Wang P. Combining the uterine depletion procedure and myomectomy may be useful for treating symptomatic fibroids. Fertil Steril 2004;82:205–10.

[4] Morita M, Asakawa Y, Uchiide I, Nakakuma M, Kubo H. Surgery results using different uterine wall incision directions in laparoscopic myomectomy of the intramural myoma. Reprod Med Biol 2004;3:33–7.

[5] Ngeh N, Belli A, Morgan R, Manyonda I. Pre-myomectomy uterine embolization minimizes operative blood loss. Br J Obstet Gynaecol 2004;111:1139–40.

[6] Rossetti A, Paccosi M, Sizzi O, Zulli S, Mancuso S, Lanzone A. Dilute ornitin vasopressin and a myoma drill for laparoscopic myomectomy. J Am Assoc Gynecol Laparosc 1999;6:189–93.

[7] Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 31st May 2005).

[8] Fletcher H, Frederick J, Hardie M, Simeon D. A randomized comparison of vasopressin and tourniquet as hemostatic agents during myomectomy. Obstet Gynecol 1996;87:1014–8.

[9] Ginsburg ES, Benson CB, Garfield JM, Gleason RE, Friedman AJ. The effect of operative technique and uterine size on blood loss during myomectomy: a prospective randomized study. Fertil Steril 1993;60:956–62.

[10] Kimura T, Kusui C, Matsumura Y, Ogita K, Isaka S, Nakajima A, et al. Effectiveness of hormonal tourniquet by vasopressin during myomectomy through vasopressin V1a receptor ubiquitously expressed in the myometrium. Gynecol Obstet Investig 2002;54:125–31.

[11] Sapmaz E, Celik H, Altungil A. Bilateral ascending uterine artery ligation vs tourniquet use for hemostasis in cesarean myomectomy. A comparison. J Reprod Med 2003;48:950–4.

[12] Sapmaz E, Celik H. Comparison of the effects of the ligation of ascending branches of bilateral arteria uteria with tourniquet method on the intra-operative and post-operative hemorrhage in abdominal myomectomy cases. Eur J Obstet Gynecol Reprod Biol 2003;111:74–7.

[13] Assaf A. Adhesions after laparoscopic myomectomy: effect of the technique used. Gynaecol Endosc 1999;8:225–9.

[14] Frederick J, Fletcher H, Simeon D, Mullings A, Hardie M. Intramyometrial vasopressin as a haemostatic agent during myomectomy. BJOG 1994;101:435–7.

[15] Celik H, Sapmaz E. Use of a single preoperative dose of misoprostol is efficacious for patients who undergo abdominal myomectomy. Fertil Steril 2003;79:1207–10.

[16] Agostini A, Ronda I, Franchi F, Bretelle F, Roger V, Cravello L, et al. Oxytocin during myomectomy: a randomized study. Eur J Obstet Gynecol Reprod Biol 2005;118:235–8.

[17] Taylor A, Sharma M, Tsirkas P, Di Spiezio Sardo A, Setchell M, Magos A. Reducing blood loss at open myomectomy using triple tourniquets: a randomized controlled trial. Int J Gynecol Obstet 2005;112:340–5.

[18] Benassi L, Lopopolo G, Pazzoni F, Ricci L, Kaihura C, Piazza F, et al. Chemically assisted dissection of tissues: an interesting support in abdominal myomectomy. J Am Coll Surg 2000;191:65–9.

[19] Zullo F, Palomba S, Corea D, Pellicano M, Russo T, Falbo A, et al. Bupivacaine plus epinephrine for laparoscopic myomectomy: a randomized placebo-controlled trial. Obstet Gynecol 2004;104:243–9.

[20] Sinha R, Hedge A, Warty N, Mahajan C. Laparoscopic myomectomy: enucleation of the myoma by morcellation while attached to the uterus. J Minim Invasive Gynecol 2005;12:284–9.

[21] Denaro V, Forriol F, Di Martino A, Denaro L, Papalia R, Caione G. Effect of a mucolytic agent on collagen fibres. An optical and

polarized light histology study. Eur J Orthop Surg Traumatol 2001;11:209–12.
[22] Fuchs AR, Fuchs F, Husslein P, Soloff MS. Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol 1984;150:734–41.
[23] Burkert H. Clinical overview of mesna. Cancer Treat Rev 1983;10 (suppl A):175–87.
[24] Farquhar CM, Brown PM, Furness S. Cost-effectiveness of preoperative gonadotrophin releasing analogues for women with uterine fibroids undergoing hysterectomy or myomectomy. BJOG 2002;109:1273–80.
[25] Lumdsden MA. Embolization versus myomectomy versus hysterectomy: which is best, when? Hum Reprod 2002;17: 253–9.