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A randomised controlled trial comparing GnRH antagonist Cetrorelix with GnRH agonist Leuprorelin for endometrial thinning prior to transcervical resection of endometrium

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Objectives To compare the effectiveness of leuprorelin and cetrorelix, when used as preoperative endometrial thinning agents prior to transcervical resection of endometrium (TCRE).

Design A prospective, double-blind randomised controlled trial.

Setting Gynaecological department of a UK district general hospital.

Participants A total of 106 premenopausal women with dysfunctional uterine bleeding, undergoing TCRE.

Interventions Women were equally randomised to 3.75 mg of leuprorelin acetate (3–4 weeks) or 3 mg cetrorelix (4–7 days) prior to TCRE. About 1 ml saline was given as placebo in both arms.

Main outcome measures Amenorrhoea rate at 6 months, endometrial thickness using transvaginal ultrasound on the day of operation.

Results A total of 100 women completed the trial with no loss to follow up. Amenorrhoea rate at 6 months after surgery was high in both groups (80% cetrorelix and 84% leuprorelin) with no statistical significance. All endometrial outcome measures including endometrial thickness on ultrasound, histology and operative appearance were more favourable in leuprorelin group as compared with cetrorelix (P values 0.013, <0.001 and 0.003 respectively). More women in leuprorelin group had hot flushes as compared with cetrorelix (15/50 versus 6/50; $P = 0.047$). No significant differences were seen in other outcome measures.

Conclusions In dosages used, leuprorelin produced more consistent thinning of the endometrium as compared with cetrorelix, although this did not make any significant difference to operative or menstrual outcomes. The endometrial thinning effect with cetrorelix does appear to be more favourable than that seen at postmenstrual phase in other studies. The optimum (possibly higher) dosage of cetrorelix for this purpose has not yet been established.

Keywords Cetrorelix, leuprorelin, endometrial preparation, TCRE, randomised controlled trial.

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Introduction

Transcervical resection of endometrium (TCRE) is now a recognised form of surgical treatment for women with dysfunctional uterine bleeding where medical treatment has failed. It offers a less radical, day-case surgical alternative to hysterectomy for these women. Although there has been a recent insurgence of various second generation modalities of endometrial ablation, where preoperative endometrial preparation is generally not used, there is still a special place for TCRE, which has a higher amenorrhoea rate in experienced hands and also allows submucous fibroids to be resected at the same time. Complete endometrial removal or destruction is one of the most important determinants of treatment success and therefore surgery is said to be most effective if undertaken when endometrial thickness is less than 4 mm, in the immediate post-menstrual phase.[1] However, due to logistic problems in reliably arranging surgery for this time, agents to prepare the endometrium are frequently used prior to TCRE.

Gonadotrophin-releasing hormone (GnRH) agonists are currently the most commonly used endometrial thinning agents.[2] They cause continuous stimulation of the GnRH receptor, producing an initial period of hypersecretion of typically 2 weeks followed quickly by pituitary desensitisation

and arrest of gonadotrophin secretion by a post-receptor mechanism, which is still not clear.[3] The initial hypersecretion however, induces a 'flare up' effect, which is responsible for adverse effects such as premenstrual symptoms, and because of the period of pituitary desensitisation, it has to be given at least 3 weeks preoperatively to obtain the desired effect on the endometrium, thus making the treatment period longer. Up to 25% of women on single dose of GnRH agonist and 64% of those on two doses suffer from hot flushes during the treatment period.[4] Hence, an ideal endometrial-thinning agent is yet to be found.[2]

GnRH antagonists, unlike the agonistic analogues, do not induce an initial stimulation of gonadotrophin release but causes immediate and rapid, reversible and dose-dependent suppression of gonadotrophin secretion by competitive receptor occupancy of GnRH receptor.[5] As a result, the onset of action and treatment period is significantly shorter with reduced incidence of adverse effects. GnRH antagonists are now at an advanced stage of clinical development, with acceptable pharmacokinetics, safety and commercial profiles. They are currently licensed only for use in assisted conception and prostatic cancer, although all other indications for GnRH agonist desensitisation may also prove to be indications for GnRH antagonists. In fact, application in endometriosis, fibroids and gynaecological cancers are already being explored.[6–8] Because of their rapid and reversible effects, with shorter treatment period and better adverse-effect profile, GnRH antagonists may have a promising role as preoperative endometrial thinning agents. They can be easily administered during the preoperative assessment visit within 1 week of the operation, thereby avoiding two visits to hospital or an extra visit at the primary care level. This would also allow for arrangement of operations at shorter notice, an advantage from convenience point of view and also a welcome solution to the women as well as local general practitioners. However, there are no relevant published studies to this date and so this study aimed to determine their efficacy in endometrial thinning prior to TCRE.

Cetrorelix acetate is a potent, hypoallergenic GnRH antagonistic analogue and was the first of its kind to be licensed for clinical use. Clinical trials with cetrorelix in women have mostly been performed in relation to assisted conception techniques where it is known to prevent a premature gonadotrophin surge in women undergoing controlled ovarian stimulation, allowing the follicles to mature for planned oocyte collection.[9–12] Phase 2 clinical trials have established that the onset of luteinising hormone (LH) suppression is approximately 1 hour with the minimal effective dose of 3 mg and the suppressive effect lasts for 4–6 days.[13–15]

There is, however, a lack of published literature on whether cetrorelix would be equally effective when given at all phases of spontaneous cycles. We, therefore, first conducted a pilot study of 10 women to observe the effect of a single 3 mg, subcutaneous dose of cetrorelix on the endometrium when administered at any phase of the menstrual cycle; the injection was given 4–8 days before surgery in premenopausal women undergoing hysteroscopy or hysterectomy. Six women were in the luteal phase and four in follicular phase. All but one woman had withdrawal bleeding of varying degrees within 48 hours of the injection. The participant who did not have any withdrawal bleeding was in early follicular phase, with an endometrial thickness (double layer) of 2.5 mm on transvaginal scanning (TVS). The double-layer endometrial thickness for the others ranged from 2 to 7 mm when scanned up to 8 days of the injection. The serum estradiol and LH levels remained suppressed up to the sixth day, being lowest on day 4 as expected. We, therefore, concluded that a single subcutaneous dose of 3 mg cetrorelix when given 4–7 days before TCRE could reliably induce withdrawal bleeding in most women, possibly bringing about the desired effect on the endometrium as needed for the procedure. With this background, we proceeded with the randomised controlled trial.

Methods

This prospective, double-blinded, randomised controlled trial was conducted in the Gynaecological Unit at the Royal Shrewsbury Hospital, between October 2003 and December 2005. The Shropshire Ethics Committee approved the study and a woman was considered eligible for the study if she was premenopausal and had opted for TCRE following appropriate selection and counselling for failed medical treatment for dysfunctional uterine bleeding. These women had normal smear history, with no concurrent gynaecological problems and had no desire for further children. As per unit policy, women aged 40 years and above had endometrial biopsy performed and those with clinically enlarged uterus also had a pelvic ultrasound scan. Women with uterine size equivalent to or more than 12 weeks of pregnancy, previous TCRE, those with menopausal symptoms and significant medical problems or severe allergic reactions were excluded from the study. Those with submucous fibroids less than 5 cm and nonatypical hyperplasia on endometrial biopsy were included in the study. Women on hormonal medications or MIRENA intrauterine system (IUS) were advised to discontinue the treatment 3 months before the procedure and were prescribed other nonhormonal preparations to control their bleeding.

Suitable women for the trial were identified from the waiting list and consecutively from the menorrhagia clinic, with detailed patient information leaflets sent out after telephone conversation or given in the clinic. Women willing to participate in the trial attended the hospital twice before the operation; the first visit at 3–4 weeks preoperatively and second visit at 4–7 days before surgery, which is the usual preoperative assessment visit.

The consenting women were allocated to receive either 3.75 mg (1 ml) leuprorelin acetate (control group) or 3 mg

(3 ml) cetrorelix acetate (experimental group) to prepare the endometrium. Leuprorelin was given 3–4 weeks and cetrorelix 4–7 days before the operation. All women also received an additional injection of 1-ml saline as placebo to allow double blinding and all injections were administered subcutaneously by a designated trial nurse. Hence, those allocated to control group received leuprorelin during the first visit and saline during the second visit. The experimental group received saline at the first visit and cetrorelix during the second visit (Figure 1).

The main objective of the study was to explore the effectiveness of cetrorelix as an alternative preoperative endometrial-thinning agent, in comparison with the standard treatment using leuprorelin. The hypothesis to be tested was

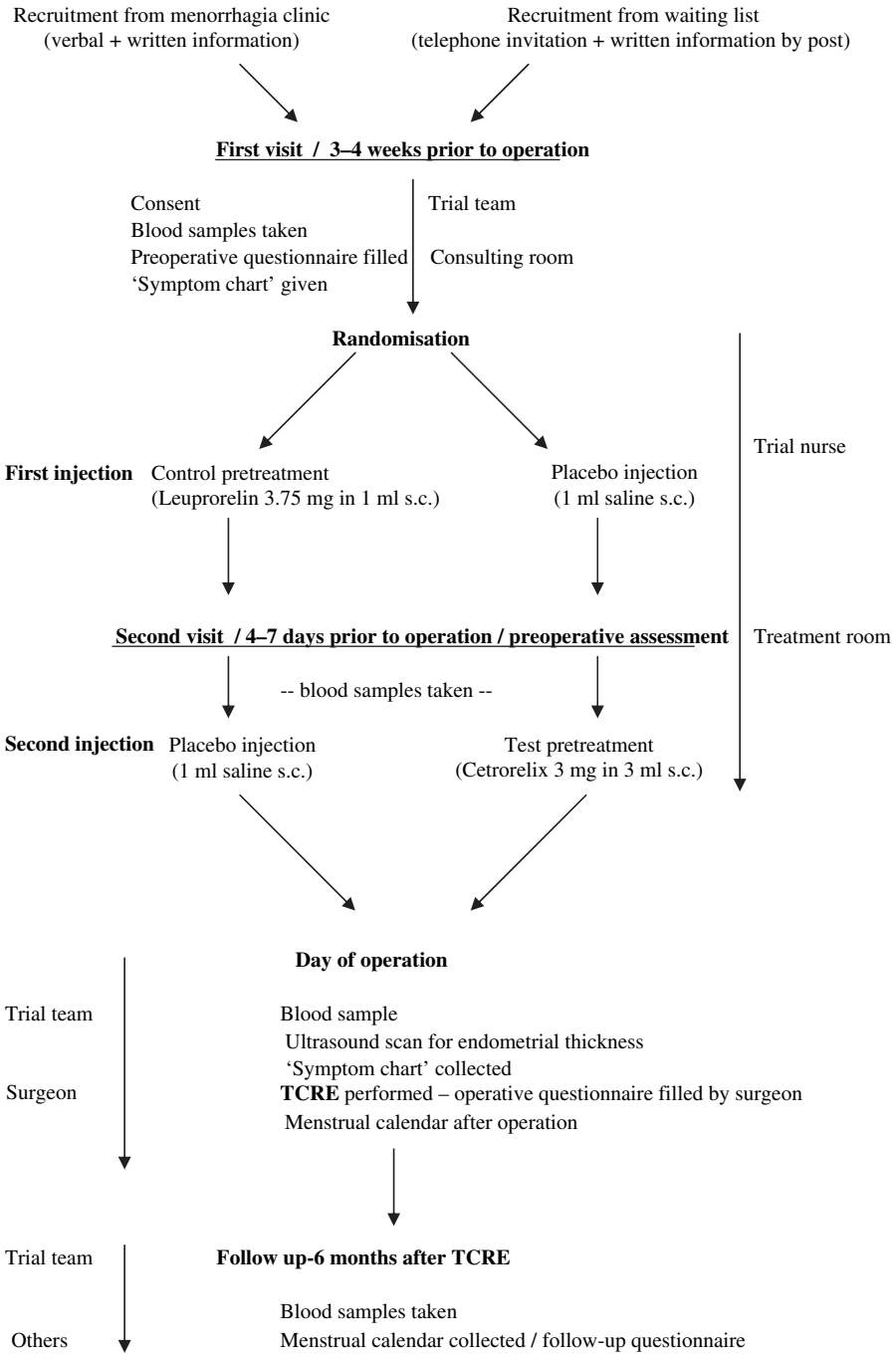

Figure 1. Study flow chart.

that cetrorelix given 4–7 days preoperatively would achieve similar endometrial thinning effect as leuprorelin given 3–4 weeks prior to the procedure with better adverse-effect profile.

The primary end points were amenorrhoea rate at 6 months after surgery (defined as no bleeding for 3 or more months, including occasional spotting) and endometrial thickness (single layer in mm) as measured on TVS on the day of surgery. The secondary end points included intraoperative and histological assessment of the endometrium, drug adverse-effect profile, biochemical evidence of suppression and surgical parameters such as duration of operation, the operative view, blood loss, fluid deficit, complication rate and overall patient satisfaction with respect to improvement in menstrual flow at 6 months following surgery. All these end points were to be compared between the two intervention groups.

Overall amenorrhoea rate following TCRE (with GnRH agonist pretreatment) from different studies ranged from 40 to 50%,[16–18] although data from our own practice at Royal Shrewsbury Hospital exceeded 70% (unpublished 12-year audit report). Based on this, statistical advice was obtained from North Staffordshire University (MF) and a sample size of 100 women, with 50 in each arm was calculated to provide the study 80% power to detect 20% fall in the 'no bleed' rate from the standard treatment, with two-sided significance set at 5% (alpha). Allowing for a 10% loss of follow up, we aimed to recruit 110 women.

A randomisation list was prepared using a computer-generated, 1:1 block randomisation schedule from North Staffordshire University (M.F.). This list was kept by the designated trial nurse (Y.D.) in the treatment room under lock and key for her perusal, and a copy was also forwarded to the local ethics committee.

The process of random allocation and assignment of treatment was performed by the trial nurse in order of recruitment according to the randomisation list. During recruitment, while the participant was seen by one of the investigators in the consulting room, the trial nurse prepared the allocated injection in a separate treatment room. Once prepared, the injection was placed behind a curtain and the participant was then brought into the treatment room. The woman was advised to lie down in semi-prone position on a couch facing the wall and the injection administered by the trial nurse in the gluteal region. Injections given were, therefore, blinded to the participants, investigators and surgeons. Apart from also helping with blood samples, the trial nurse was not involved in the measurement of any outcomes or analysis. The randomisation list was forwarded to the main investigator (K.B.) only after the completion of follow-up process.

During the first visit, that is, 3–4 weeks before operation, the participants were first seen by one of the investigators in the consulting room. Informed and written consent was obtained from eligible women. Baseline information including age, parity, body mass index, menstrual cycle and date of last menstrual period was recorded, and blood samples for serum follicular stimulating hormone (FSH), LH, estradiol and progesterone obtained. The trial nurse was informed and once she was ready with the injection, the participant was taken into the treatment room and administered the first injection. A 'symptom questionnaire' was given to record any adverse effects and bleeding, which was to be collected on the day of surgery. An appointment was made for the participant to be seen by the trial nurse for the second visit, that is, 4–7 days before operation and also for preoperative assessment.

For the second visit, the trial nurse similarly prepared the second injection in the treatment room before bringing the woman in. Further blood samples were taken for serum FSH, LH, oestradiol and progesterone, and the second injection was administered. The participants were then sent for preoperative assessment. On the day of operation, endometrial thickness was measured using transvaginal ultrasound (TVS) by one of the investigators (K.B., B.K. or B.B.) who were all competent to do so. The double-layer endometrial thickness in millimetres (mm) was measured at its thickest point (approximately 1–2 cm from the fundus) in sagittal plane and the result halved to derive the single-layer thickness. The location and size of any fibroids if present were also noted. Symptom questionnaires were collected and blood samples for serum estradiol and serum FSH were taken.

Surgery was performed by established, experienced surgeons in most women and trainees under direct supervision in some, as usual. TCRE was performed using a continuous flow hysteroscope and resectoscope loop as per usual practice for the surgeon concerned, generally involving complete resection followed by roller ball diathermy. The duration of surgery was measured from the first insertion of speculum to last removal of the resectoscope, excluding time for additional procedures such as sterilisation. Apart from documenting intraoperative appearance of the endometrium and other operative details, the surgeons were also asked to comment on the likely preoperative thinning agent received by the patient. The length of the uterine cavity as measured by uterine sound and the presence of any endometrial polyps, submucous fibroids and other abnormality was also noted.

The irrigation fluid used was sorbitol (4%). All effluent fluid was collected and amount of fluid deficit was calculated by subtracting the effluent volume from the volume instilled. Any specific postoperative problem needing overnight observation was recorded and also the need for intrauterine balloon for tamponade. All women were given prophylactic antibiotics (cephalexin and metronidazole) for 7 days to prevent postoperative infection as per usual practice. A menstrual calendar was given to all women to record their subsequent menstrual symptoms.

Women were followed up 6 months after the operation in the menorrhagia clinic as usual practice. The menstrual calendars were collected and after discussion with the woman, the attending doctor filled in the '6 months follow-up'

questionnaires, which was clipped to the front of the notes. The effect of operation on their menstrual bleeding pattern and on any existing dysmenorrhoea or onset of new pain was recorded. Overall patient satisfaction from the operation was directly asked on a Likert's 6-point scale. Final blood samples for serum FSH and estradiol were taken to rule out the onset of menopause in amenorhoeic women. A few of those who failed to attend their follow-up appointment were contacted on telephone by one of the investigators. Further details on unsatisfied women were obtained at a later stage and any additional interventions such as hysterectomy, repeat ablation or medical treatment were also recorded. The randomisation list was forwarded to the main investigator (K.B.) after the follow up of the last participant and codes finally broken for analysis.

Data were entered into a personal computer on a spreadsheet program by the main investigator (K.B.) contemporaneously and later transported to SPSS windows (version 13; SPSS Inc., Chicago, IL, USA) and R statistics software for analysis by the statisticians (MF and A.G.). The analysis was on 'intention-to-treat' basis. Chi- square test and Fisher's exact test was used to compare proportions between two groups. *P* values with odds ratios and 95% confidence intervals were calculated. Paired *t* test was used to compare paired variables and two samples *t* test to compare independent variables. Where normality assumptions were violated, equivalent nonparametric tests were used; Mann–Whitney *U* test for independent variables and Wilcoxon signed rank test for dependent variables. Data on ultrasound endometrial thickness were log-transformed to correct for skewness; mean values were calculated from the log-transformed data and analysed using independent samples *t* test.

Results

The recruitment of participants began in October 2003 and ended in June 2005. The follow-up period continued till the end of December 2005. The CONSORT scheme of reporting a randomised controlled trial was adhered to. CONSORT diagram showing the flow of participants through each stage is shown in Figure 2.

Of the 110 consecutive eligible women, four declined to participate since they were not keen to have an extra injection. A total of 106 consecutive women undergoing TCRE were randomised to receive either leuprorelin or cetrorelix before their operation. There were six drop outs, three in each group: operation was cancelled in five women having received both the injections due to newly detected medical problems (three raised blood pressure, one hyperglycaemia and one acute illness) and one participant from the leuprorelin group decided not go ahead with the operation a few days after her first injection for personal reasons. The minimum required total of 100 women was operated upon, with 50 in each group and none lost to follow up. All 100 women were analysed. The baseline characteristics including age, parity, body mass index, menstrual pattern and grade of surgeon were well matched for both groups. Six women in cetrorelix group had fibroid uterus as compared with four in leuprorelin group ($P = 0.740$). Also, four women in cetrorelix group had endometrial polyps as compared with two in leuprorelin group ($P = 0.677$). Two women in cetrorelix group had bicornuate uterus and the uterine cavity length was also longer in cetrorelix group (difference in mean = 0.94 cm; $P = 0.001$; 95% CI 0.443–1.533) (Table 1). Nearly all patients were Caucasian.

Menstrual outcome

The details of menstrual outcome measures including bleeding pattern, pain and overall satisfaction are shown in Table 2.

The amenorrhoea rate at 6 months after surgery was high in both groups (40/50, 80% for cetrorelix and 42/50, 84% for leuprorelin, with no statistical significance between the two groups ($P = 0.482$; OR: 1.181; 95% CI: 0.415–3.363). Of these, three women in cetrorelix group and six women in the leuprorelin group had occasional spotting, not needing any sanitary protection. Six women in cetrorelix group experienced no difference in the menstrual bleeding or the bleeding was worse as compared with three in the leuprorelin group (12 versus 6%), although this difference was not found to be significant statistically ($P = 0.233$). However, the odds of bleeding being the same or worse as compared with lighter and/or amenorrhoeic in cetrorelix group are 2.18 times greater than with leuprorelin (OR: 2.186; 95% CI: 0.515–9.285).

There was no significant difference in menstrual pain in both the groups ($P = 0.974$), with equal proportions documenting either improvement or worsening of pre-existing menstrual pain and onset of new pain. Overall satisfaction from the operation was high in both groups with no statistical significance between the two groups difference (42/50, 86% for cetrorelix; 46/50, 92% for leuprorelin; OR: 0.522; 95% CI 0.143–1.91; $P = 0.32$).

Endometrial thickness measures

All outcome measures on endometrial thickness on the day of surgery were statistically more favourable in women who received leuprorelin as compared with cetrorelix, but these were not clinically significant; endometrial thickness was <4 mm in all women, except those with hyperplasia (Table 3).

All participants had transvaginal ultrasound scanning for endometrial thickness on the day of the procedure. The results on six women were not available (three in each group). Another six women had endometrial polyps (four in cetrorelix and two in leuprorelin) and these were excluded from analysis on endometrial thickness. There were six other women with endometrial hyperplasia (five cetrorelix and one leuprorelin) and the data were analysed both by including and excluding them. In the first part of analysis, which included women with endometrial hyperplasia, a total of 43 women

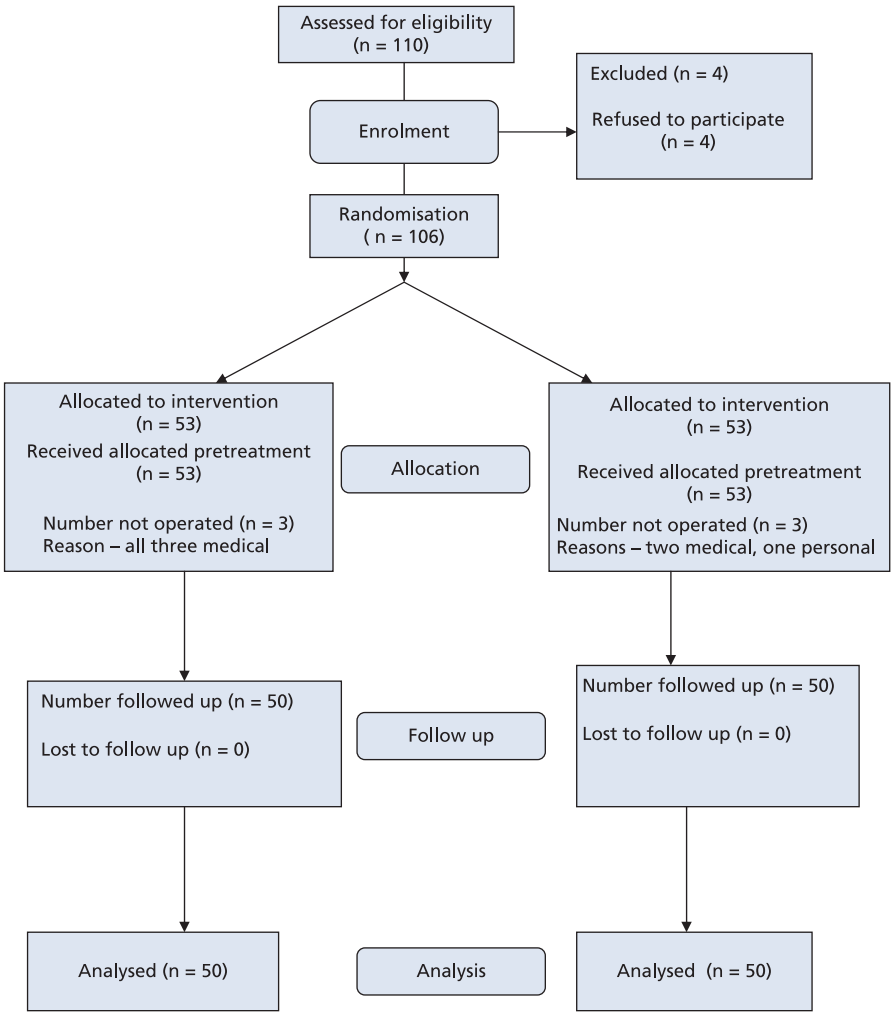

Figure 2. Flow of participants – CONSORT diagram.

in cetrorelix and 45 in leuprorelin were analysed; the mean single-layer endometrial thickness for cetrorelix group was 2.50 mm as compared with 1.96 mm for leuprorelin group. The difference in means of the 'log-transformed data' was statistically significant (mean difference 0.25 mm; 95% CI for mean difference 0.04–0.47; $P = 0.017$).

In the second part of the analysis that excluded women with hyperplasia, the mean single-layer endometrial thickness for cetrorelix group (39 women, one woman also had polyp) was 2.35 mm as compared with 1.82 mm for leuprorelin group (44 women). The mean difference of the 'log-transformed' data (0.25 mm; 95% CI: 0.05–0.45) was again statistically significant ($P = 0.013$).

Histology report was available on all women but six with endometrial hyperplasia were excluded from the comparative analysis. The endometrium was more likely to be inactive or basal in the leuprorelin group (36/49, 73%) than in the cetrorelix group (17/45, 38%). The odds of histology being other than inactive or basal for cetrorelix is 4.34 times as compared with leuprorelin (OR: 4.34, 95% CI: 1.9–10.94; $P \leq 0.001$). In women with endometrial hyperplasia where a biopsy was taken before TCRE, the hyperplasia was persistent in histology of the endometrial chippings.

Similarly for intraoperative appearance of endometrium, six women with hyperplasia were excluded (five cetrorelix and one leuprorelin). The endometrium was documented as thick in 13 of 45 women in the cetrorelix group (29.5%) as compared with 3 of 49 in the leuprorelin group (6%), with a significant difference between the two groups (OR: 6.43; 95% CI: 1.69–24; $P = 0.003$). Based on intraoperative appearance of the endometrium, when asked to comment on the likely pre-treatment received, up to 41% surgeons were incorrect.

Surgical parameters

Overall operative view was good in most participants (47/50, 94% in cetrorelix group and 49/50, 98% in leuprorelin

Table 1. Baseline characteristics in both groups

Characteristics	Cetrorelix ($n = 50$)	Leuprorelin ($n = 50$)	*P* value
Mean age, years (SD)	40.04 (5.27)	41.46 (5.8)	
Parity (no. of children), *n* (%)			
0	2 (4)	3 (6)	NS
1–2	18 (36)	21(42)	
3>	30 (60)	26 (52)	
Body mass index, mean (SD)	27.8 (5.08)	27.46 (3.84)	NS
Menstrual cycle (pattern), *n* (%)			
Regular and heavy	21(42)	27 (54)	
Irregular and heavy	29 (58)	23 (46)	NS
Uterine cavity			
Length in cm, mean (SD)	9.19 (1.45)	8.25 (1.23)	$P = 0.001$
Bicornuate, *n* (%)	2 (4)	0 (0)	
Septum, *n* (%)	0 (0)	1 (2)	
Polyps, *n* (%)	4 (8)	2 (4)	$P = 0.677$
Fibroid uterus, *n* (%)			
None	44 (88)	46 (92	$P = 0.740$
Total	6 (12)	4 (8)	
Submucous	5 (10)	3 (6)	
Grade of surgeons, *n* (%)			
Consultant	44 (88)	43 (86)	NS
Trainee	6 (12)	7 (14)	

NS, not significant.

group), there being no significant difference between the two groups ($P = 0.617$; OR: 0.32; 95% CI: 0.32–3.18) (Table 4). The mean operative times for both the groups were also similar (31.9 minutes for cetrorelix and 29.6 minutes for leuprorelin; mean difference 2.260 minutes; 95% CI: –1.159 to 5.679; $P = 0.193$).

One woman in cetrorelix group sustained uterine perforation during cervical dilatation and one woman from leuprorelin had significant cervical resistance resulting in traumatic dilatation with poor operative view.

The median fluid deficit for cetrorelix was 300 ml compared with 250 ml for leuprorelin, with no significant

Table 2. Menstrual outcomes/satisfaction

	Cetrorelix ($n = 50$)	Leuprorelin ($n = 50$)	Test used/*P* value/OR/95% CI
Bleeding, *n* (%)			
Amenorrhoea*	40(80)	42 (84)	Fisher's exact test/$P = 0.482$/1.181/0.415–3.363
Hypomenorrhoea**	4 (8)	5 (10)	
Amenorrhoea + hypomenorrhoea	44 (88)	47 (94)	
Same or worse	6 (12)	3 (6)	$P = 0.233$/2.186/0.515–9.285
Menstrual pain, *n* (%)			
Better	16 (32)	16 (32)	Chi-square test/$P = 0.974$
Worse/persistent	7 (14)	8 (16)	
New pain	4 (8)	3 (6)	
No pain before/after	23 (46)	23 (46)	
Satisfaction, *n* (%)			
Satisfied	43 (86)	46 (92)	Chi-square test/$P = 0.320$/0.522/0.143–1.910
Unsatisfied	7 (14)	4 (8)	

*No periods for three or more months, including occasional spotting (of these, three in cetrorelix group and six in leuprorelin group had occasional spotting only).
**Lighter periods or cyclical spotting.

Table 3. Endometrial parameters

	Cetrorelix	Leuprorelin	Estimated difference, (95% CI), *P* value
Single-layer endometrial thickness (ultrasound)			
Hyperplasia included (*n*)	43	45	Independent *t* test; mean difference (log-transformed data)
Mean, mm (SE)	2.50 (0.19)	1.96 (0.20)	0.25 (0.04–0.47); $P = 0.017$*
Hyperplasia excluded (*n*)	39**	44	
Mean mm (SE)	2.35 (0.17)	1.82 (0.15)	0.25 (0.05–0.45); $P = 0.013$*
Endometrium at operation, *n* (%)* **			
Thin	32 (71.1)	46 (93.9)	Chi-square test; OR 6.43 (1.69, 24); $P = 0.003$*
Thick	13 (28.9)	3 (6.1)	
Total (*n*)	45	49	
Histology, *n* (%) * **			
Basal/inactive	17 (37.75)	34 (69.39)	Chi-square test; OR 4.34 (1.9, 10.94); $P \leq 0.001$*
Other	28 (62.22)	15 (30.61)	
Total (*n*)	45	49	

*Significant values.
**One with polyp and hyperplasia.
***Hyperplasia excluded (five cetrorelix and one leuprorelin).

difference in the medians ($P = 0.641$). Five women had fluid deficit of more than 1500 ml (three in cetrorelix and two in leuprorelin); operation was completed in all and only one woman needed a single dose of frusemide with overnight observation (in cetrorelix group with uterine perforation; 2000 ml of fluid deficit).

Clinical estimation of blood loss was not possible although none of the participants in both groups required blood transfusion. Intrauterine balloon was however inserted to arrest oozing after TCRE in 12 women (seven in cetrorelix and five in leuprorelin); two women in each group needing intrauterine balloon had submucous fibroids. Most of these were

Table 4. Operative parameters

	Cetrorelix group* (*n* = 50)	Leuprorelin group** (*n* = 50)	Test used, Estimated difference, 95% CI, *P* value
Operating time in minutes, mean (SD)	31.94 (8.74)	29.68 (8.47)	Independent samples test; mean difference 2.260 (−1.159 to 5.679); $P = 0.193$
Operative view, *n* (%)			Fishers exact test; OR: 0.32 (0.32–3.18); $P = 0.617$
Good	47 (94)	49 (98)	
Poor	3 (6)	1(2)	
Fluid deficit			
Median (range), ml	300 (0–2000)	250 (0–2000)	Mann–Whitney test, $P = 0.641$
>1500 ml, *n* (%)	3 (6)	2 (4)	
IU balloon, *n* (%)	7 (14%)	5 (10%)	NS
Submucous fibroid, *n*	2	2	
Complications, *n* (%)			
Uterine perforation	1 (2)	0	NS
Traumatic dilatation of cervix	0	1(2)	
Fluid deficit >1500 ml	2 (4)***	2(4)	
Total complications	3 (6)	3 (6)	

IU, intrauterine; NS, not significant.
*Six with fibroid uterus and two bicornuate uterus
** Four with fibroid uterus
***Excludes one with uterine perforation

operated upon by trainees and balloons inserted as a precaution. The balloon was removed within 2–4 hours and all were discharged home the same day.

Overall complication rates are similar for both groups (3/50, 6% for cetrorelix and 3/50, 6% for leuprorelin).

Tolerability

In terms of adverse effects, more women in leuprorelin group experienced hot flushes (15/50, 30%) as compared with cetrorelix (6/50, 12%) (Table 5). This difference in proportions was statistically significant ($P = 0.0478$; OR: 3.107; 95% CI: 1.009–10.838).

Local skin irritation in the cetrorelix group was higher (8/50, 16%) as compared with leuprorelin (3/50, 6%) but this was not statistically significant ($P = 0.199$; OR: 0.338; 95% CI: 0.054–1.528). However, one particular woman in cetrorelix group did have a fairly severe skin reaction needing antihistaminic treatment. Again, on combining all adverse effects, there was no significant difference in the two groups (20/50, 40% for leuprorelin; 13/50, 26% for cetrorelix; $P = 0.201$; OR: 1.885; 95% CI: 0.750–4.869).

Also of note is that significant proportion of women (15/50) in the cetrorelix group experienced some adverse effects, predominantly hot flushes, after saline injections (before receiving cetrorelix); 6/50 in the leuprorelin group also experienced adverse effects after saline injections (2–3 weeks after receiving leuprorelin).

Other outcome

Biochemical evidence of estrogen suppression was more obvious in women who received leuprorelin than cetrorelix as determined from serum estradiol and FSH levels taken just before administration of the injections and on the day of operation. Fall in both serum FSH and estradiol levels in the leuprorelin group was seen in 38/46 women, 82.6%; in cetrorelix group, fall in estradiol levels was seen in 25/42 women (59.5%). There was no clear pattern of change in serum FSH levels in cetrorelix group. The difference in the proportion of women showing fall in serum estradiol levels in both the groups is statistically significant (difference in proportions 0.231; 95% CI: 0.046–0.416). There was also significant difference in the median serum estradiol levels taken on the day of operation; 88.50 pmol/l (range 18–800) for leuprorelin and 146.50 pmol/l (range 1–1107) for cetrorelix ($P \leq 0.001$).

Surprisingly, there was no consistent pattern seen in the withdrawal bleeding following cetrorelix injection unlike the pilot study; only 20/46, that is, 48.5% women had some withdrawal bleeding after its administration.

Further intervention

Seven women (four cetrorelix and three leuprorelin) were either on the waiting list or had hysterectomy at the end of follow-up period. There was no significant difference between the two groups ($P = 0.695$; OR: 1.36; 95% CI: 0.29–6.36). None had repeat ablation. Another seven women (four cetrorelix and three leuprorelin) were awaiting further review for pain or bleeding.

Discussion

The role of TCRE for treatment of menorrhagia is becoming limited due to availability of second generation endometrial ablation procedures and the levonorgestrel intrauterine system (MIRENA). However, it is still being used by a small number of enthusiasts and is particularly useful in women with submucous fibroids. TCRE is still the primary endometrial ablative procedure performed at the Royal Shrewsbury Hospital and majority performed as day-case. The current process of care for women having TCRE involves a visit at their local GPs surgery 3–4 weeks before the operation for a single injection of GnRH agonist to prepare the endometrium. Women are then seen at the hospital about 1 week before the operation for their preoperative assessment. This process requires careful planning with proper communication between the hospital and GPs, and occasionally operations have been postponed because the injections have not been given as planned.

The question of whether to prepare or not to prepare the endometrium may be argued by some critics and hence the

Table 5. Adverse effects

Adverse effects	Cetrorelix ($n = 50$)	Leuprorelin ($n = 50$)	Difference in proportions, 95% CI, *P* value, OR, Fisher's exact test	Saline ($n = 100$)
Hot flushes, *n* (%)	6/50 (12)	15/50 (30)	0.18; 0.0043–0.355, $P = 0.0478$, OR 3.107 (1.009–10.838)	21/100
Skin irritation, *n* (%)	8/50 (16)*	3/50 (6)	0.10; −0.241 to 0.041, $P = 0.199$, OR 0.338 (0.054–1.528)	3/100
Nonspecific adverse effects, *n* (%)	2/50 (4)**	2/50 (4)		5/100
Total adverse effect, *n* (%)	13/50 (26)	20/50 (40)	0.14; −0.0623 to 0.342, $P = 0.201$, OR 1.885 (0.750–4.869)	29/100

*One woman also had hot flushes.
**Two women also had hot flushes.

need for an agent to thin the endometrium.[16] There is now good evidence to show that pre-thinning the endometrium enables even experienced surgeons easier, faster surgery with higher amenorrhoea rates 6 months after surgery compared with those who had the procedure performed in the post-menstrual phase after receiving placebo injections.[2,17]

Our pilot study, although limited in not being controlled, confirmed that a single 3 mg dose of cetrorelix could reliably induce a withdrawal bleeding within 2–3 days, irrespective of the phase of menstrual cycle. Therefore, the same dosage was used in the main study. GnRH antagonist activity of cetrorelix is dose dependent, so it is possible to adjust the dose to obtain the required level of inhibition. A larger dose of 5 mg although more effective, is likely to be limited in terms of adverse effects such as skin irritation and hot flushes. Daily doses of 0.25 mg of cetrorelix would have the advantage of better adverse-effect profile as well as efficacy but would be less attractive to the women and health providers for obvious reasons.

To our knowledge, an overall amenorrhoea rate of 82% and amenorrhoea + hypomenorrhoea rate of 91% seen at 6 months in this study is one of the highest reported in literature,[19] although it remains to be seen whether this will be maintained at the end of 3 years, when we intend to report our longer term outcomes including hysterectomy rates to allow proper comparisons. Our overall complication rates appear lower than that reported in literature.[20]

It is interesting to note that although all the endometrial measurements were more favourable with leuprorelin pre-treatment as compared with cetrorelix, this did not affect the amenorrhoea or no bleed rate at 6 months or any of the operative outcome measures. This is likely to be due to the relatively thin endometrium (mean 2.5 mm, range 0.7–6.0 mm including hyperplasia) seen in all cetrorelix pre-treated women. Indeed, more women in cetrorelix group had endometrial polyps, fibroids, bicornuate uterus, hyperplasia and larger uterine cavities, which could explain for relatively more women with bleeding being same needing hysterectomy in cetrorelix group as compared with leuprorelin group although this was not statistically significant.

Endometrial thickness (single layer) seen in our study appears to correlate well with other studies where only one dose of GnRH agonist was used.[2,17] Endometrial results obtained with cetrorelix pre-treatment, however, does appear to be better than placebo pre-treated women in postmenstrual phase seen in other studies, although ideally a placebo arm in our study would have confirmed this. The mean single-layer endometrial thickness following cetrorelix pre-treatment seen in our study (2.50 mm) is thinner than that measured during the postmenstrual phase reported by Donnez *et al.* (3.53 mm for placebo group as compared with 1.61 mm for goserelin treated).[17] Also, in the same study, the histological appearance of endometrium yielded atrophic glands and stroma in less than 15% of women in the placebo group (postmenstrual phase) as compared with 70% in women who had received two doses of goserelin. The endometrium was atrophic or basal in 38% of women who received cetrorelix as compared with 69% in leuprorelin group in our study. Amenorrhoea rates when TCRE was performed in placebo-pre-treated (postmenstrual) women were also statistically lower than GnRH agonist pre-treated women.[17]

The trial was offered to all consecutive women undergoing TCRE rather than a selected group and hence can be extrapolated to the general population of women undergoing endometrial ablation/resection procedures. With increasing use of the simpler second generation endometrial ablative procedures, it was anticipated that there would be problems with recruitment of participants and hence amenorrhoea rate was used to calculate the sample size to generate a smaller sample size. This limitation has been reflected in the wider 95% CIs seen with histological/operative appearance of endometrium and complication rates especially, hot flushes and hysterectomy rates.

Despite robust attempt at double blinding, some of the known adverse effects from both the treatments had a potential for revealing the pre-treatment received by each participant: prior knowledge from the pilot study that cetrorelix is likely to induce withdrawal bleeding in most women and the onset of hot flushes with leuprorelin. To avoid bias from this, the 'symptom questionnaires' were collected on the day of operation and the details were not available to the surgeons. The data on adverse effects were entered in the computer only after the completion of trial. It was interesting to note that although 30% of women in leuprorelin group experienced hot flushes, an equal number of women in cetrorelix group also experienced hot flushes after saline injections. It is difficult to explain the lack of withdrawal bleeding in 51.5% of women pre-treated with cetrorelix contrary to the pilot study. One possible explanation is that most of these women may have been in early follicular phase (as shown by thin endometrial thickness) and hence no significant withdrawal bleeding was noted following the injection.

Conclusions

TCRE remains an extremely effective procedure for women with excessive menstrual bleeding. This study showed an overall 82% amenorrhoea rate at 6 months follow up. In the dosages used, leuprorelin produced more consistent thinning of the endometrium as compared with cetrorelix, although this did not significantly affect any of the operative or menstrual outcomes. The fact that cetrorelix can be given subcutaneously within 7 days of surgery (compared with 3–4 weeks before surgery with leuprorelin and other GnRH analogues) has reduced estrogen withdrawal adverse effects and no significant reduction in menstrual and operative outcome measures establishes it as a suitable endometrial thinning agent

before TCRE. The optimum (possibly higher) dosage of cetrorelix for this purpose has not yet been established.

Contributions of authorship

B.B.: Principal investigator in charge/Head. Conceived the study idea and constructed the study design. Ethical approval process: advisory and supervisory role in the preparation of documents, conduct of the trial and preparation of this manuscript. Ultrasound examination, operating and follow-up process. K.B.: First and corresponding author of manuscript; Main investigator/coordinator as research fellow. Ethical approval process: preparation of all trial documents; recruitment, ultrasound examination, operating and follow up; data management. Y.D.: Designated 'trial nurse'/held 'randomisation list'; responsible for concealment and implementation of random allocation/assignment of treatment. Administration of all injections, helped take blood samples. A.G.: Final data analysis.

Ethical approval

A Clinical Trials Exemption certificate was obtained from Medicines and Healthcare Products Regulatory Agency (certificate number MF 800/12894, July 2003) for this trial and was approved by the Shropshire Ethical and Research committee on 23 September 2003 (03/40/RSH). Recruitment began in October 2003 and hence this trial has not been registered with www.ClinicalTrials.gov.

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