The regulation of ovarian and uterine blood flow are important aspects of reproductive physiology. Rapid and profound alterations in the vasculature of the cycling ovary have been reported and suggestions that blood flow to individual follicles may play an instrumental role in the selection and maturation of the dominant follicle in the primate (Zeleznik et al., 1991). More recent data indicates a functional relationship between blood flow and steroid output within the ovarian follicle and corpus luteum (Damber et al., 1990).

Likewise there are extensive changes in uterine vasculature apparent from histological changes which occur at puberty, in pregnancy, and following the menopause. A common feature of these diverse stages in reproductive life are significant alterations in the circulating oestrogen concentrations. This suggests that the uterine circulation appears to be under the influence of ovarian hormones (Geiss and Andersson, 1970).

Leiomyomas (fibroids) are a common pathological change found in the uterus. It is essential to be aware that when a patient is asymptomatic with the presence of fibroids, there is no need for surgery. When the patient is symptomatic and the symptoms thought to be related to the presence of the leiomyoma, then surgery is appropriate. Such surgery is recognized not to be without risk when it is associated with myomectomy and the risk is dependent upon a number of features which are summarized in Table I.

If surgery is to be embarked upon it would seem sensible to adopt adjuvant treatment in patients with uterine fibroids that would be beneficial in both reducing the size of the fibroids present as well as useful in preparing the patient for surgery and reducing blood loss during surgery. It is with these issues in mind that the role of gonadotrophin-releasing hormone (GnRH) analogues in patients with uterine fibroids, who require surgery, has been investigated in recent years.

The role of GnRH analogues in decreasing fibroid size

Several studies have now indicated that treating patients with GnRH analogues results in a reduction in the size of uterine fibroids (Coddington et al., 1986;
Table I. Risks associated with myomectomy

Operative risks not insubstantial and related to perioperative blood loss

- Increasing size of fibroid
- Presence of multiple fibroids
- Pre-operative anaemia (from associated menorrhagia)
- Post-operative ooze with resultant hematoma and adhesion formation
- Post-surgical induced infertility
- Risk of incision rupture in subsequent labour

Maheux et al., 1987). Our own data indicate that the vast majority of this reduction occurs within the first month of therapy and that most patients have achieved their near maximum reduction in size by three months of pre-treatment with a GnRH analogue (Matta et al., 1989; Williams and Shaw, 1990). Our studies have indicated that it is important to achieve suppression of circulation oestradiol concentrations to below a specific threshold for an individual to achieve this reduction in uterine size and that the level of oestrogen suppression appears to be individually determined. Further suppression within an individual over this threshold concentration does not lead to greater reduction in size.

A reduction in size of fibroids prior to surgical intervention obviously must present positive advantages for the surgical procedure as discussed in further presentations at this symposium. Of equal relevance in the preparation of the patient is the other advantages of GnRH analogue pretreatment achieved.

Use of GnRH analogues to correct pre-operative anaemia

Whilst many patients with uterine fibroids complain of increased menstrual blood loss, the majority have haemoglobin levels within acceptable ranges (>10.8 g/dl) which would not preclude surgical intervention or require pre-operative blood transfusion. However, a significant proportion of ~10% in our practice, are anaemic at presentation and the time of determining that surgery is necessary. One secondary advantage of administering GnRH analogues to such patients prior to surgery is that the majority of patients will be rendered amenorrhoeic by the degree of hypoestrogenism induced after administration of the GnRH analogue thus controlling their excessive menstrual blood loss and allowing correction of their anaemia. Data was collected on a sub-group of patients with significant anaemia who received a GnRH analogue for three months (either 3.6 mg of goserelin monthly or 3.75 mg of Decapeptyl monthly). This pretreatment resulted in correction of the anaemia prior to surgical intervention (see Table II).

This correction of anaemia during the pre-operative preparation of the fibroids by reduction in size, offers many advantages and the 3 month treatment interval does not seem an unduly excessive delay in surgery to enable such patients to be more appropriately prepared for surgery.
GnRH analogues and blood flow

Table II. Use of gonadotrophin-releasing hormone (GnRH) analogue pretreatment* to correct anaemia due to menorrhagia in patients with fibroids (n = 16). Values are expressed as means ± SD

<table>
<thead>
<tr>
<th></th>
<th>Baseline Hb (g/dl)</th>
<th>Pre-Op Hb (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.3 ± 1.7*</td>
<td>12.7 ± 0.4*</td>
</tr>
</tbody>
</table>

*Patients received either goserelin 3.6 mg or Decapeptyl 3.75 mg at monthly intervals for 3 months. paHb = haemoglobin.

Table III. Changes in uterine artery resistance index (RI) during gonadotrophin-releasing hormone (GnRH) analogue therapy*. All values are expressed as means ± SD

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>2 months</th>
<th>4 months</th>
<th>6 Weeks Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean serum oestradiol (pmol/l)</td>
<td>302 (43)</td>
<td>116 (24)</td>
<td>83 (23)</td>
<td>297 (36)</td>
</tr>
<tr>
<td>Total uterine volume (cm³)</td>
<td>656 (113)</td>
<td>487 (98)</td>
<td>386 (70)</td>
<td>501 (124)</td>
</tr>
<tr>
<td>Individual fibroid volume (cm³)</td>
<td>180 (50)</td>
<td>77 (15)</td>
<td>58 (14)</td>
<td>94 (21)</td>
</tr>
<tr>
<td>Uterine artery RI</td>
<td>0.52 (0.02)</td>
<td>0.68 (0.04)</td>
<td>0.92 (0.04)</td>
<td>0.59 (0.03)</td>
</tr>
</tbody>
</table>

*Treatment was with buserelin 400 µg three times daily intranasally.

Effects of GnRH analogue pre-treatment on uterine artery blood flow

The apparent functional relationship between utero-ovarian blood flow, follicular development and circulating oestrogen concentrations is the basis for our investigation of these aspects. In recent years, several workers (Geiss and Andersson, 1970; de Ziegler et al., 1991; Weiner et al., 1993) have demonstrated that the resistance to flow in the uterine artery declines throughout the cycle and demonstrates a negative linear correlation with rising serum oestradiol concentrations. This decrease in vascular resistance may be related to a direct vasodilatory effect of the circulating oestradiol on the uterine artery (Geiss and Andersson, 1970; de Ziegler et al., 1991) but other mechanisms may also be involved.

The known alterations in circulating oestradiol induced by administration of GnRH analogues might well then be expected to have induced effects on the uterine artery blood flow. These could be of relevance in terms of preparation of the uterus for surgery.

We therefore studied a group of patients with significantly enlarged uteri containing single or multiple uterine fibroids during pre-treatment with a GnRH analogue. All patients had an abdominally palpable uterus of 14 weeks size or greater at the commencement of analogue therapy, the analogue administered for the initial study was buserelin at a dose of 400 µg, three times daily, intranasally. Patients underwent transabdominal pulse wave Doppler measurements of their uterine arteries and in many instances of distinct vessels seen supplying individual fibroids. The scanner utilized was a ATL sector scanner with a duplex system containing a 100 Hz high pulse filter. All of the studies were performed by a single observer taking a mean of three measurements on each occasion and a calculated coefficient of variation of 3–5%. The resistance index was calculated
Figure 1. Relationship between internal artery Doppler blood flow and baseline total uterine volume (cm$^3$) (RI = resistance index).

as the peak systolic (A) minus the peak diastolic (B) divided by the peak systolic (A - B/A). Results in this cohort of patients, observed immediately prior to treatment in the follicular phase of the cycle and after 2 months and 4 months on therapy with buserelin 400 mg three times daily intranasally are tabulated in Table III.

These data clearly indicate a marked response in respect of reduced circulating concentrations of oestradiol 17β achieved with continuing administration of GnRH analogue. There is significant reduction both in total uterine volume during the time course of the study as well as of individual fibroid volumes where measurable. In association with these changes there is a significant increase in the uterine arterial resistance index (RI) after 4 months of treatment ($P < 0.01$). There is a suggestion also of an increase in the arterial resistance index (RI) within specific vessels within fibroids after 4 months pre-treatment ($P < 0.001$).

A further component to the study was a group of 16 patients with significantly enlarged uteri who were due to undergo myomectomy. In these the resistance index in the uterine artery was measured prior to commencement of a depot GnRH analogue pre-treatment 'for 3 months'. The mean values of the uterine artery resistance index in both the left and right uterine artery were plotted against uterine volume as measured ultrasonically in cubic centimetres (cm$^3$). These data are shown in Figure 1 and demonstrate an inverse correlation between the size of the uterus at pretreatment and the uterine artery resistance index (RI).

These data suggest that GnRH analogue pretreatment could be viewed as being even more beneficial in patients with a larger uterus because of their increased blood flow as evidenced by their lower uterine artery resistance index values.

Whether these alterations in uterine artery resistance index readings during GnRH analogue pre-treatment are of clinical relevance was further assessed in the next part of our study in which blood loss at surgery was measured accurately.
Table IV. Measured blood loss at myomectomy: effect of gonadotrophin-releasing hormone analogue (GnRHa) pretreatment

<table>
<thead>
<tr>
<th>Controls matched for post-GnRHa uterine size</th>
<th>GnRHa pretreated X weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15</td>
</tr>
<tr>
<td>Blood loss at surgery (ml)</td>
<td>794 ± 103*</td>
</tr>
<tr>
<td>Blood transfusion (number of patients)</td>
<td>8*</td>
</tr>
</tbody>
</table>

*P <0.05.

Blood loss measurements at surgery: effect of GnRH analogue pretreatment

This component of the study consisted of a group of 30 patients with significantly enlarged fibroid uteri and symptoms justifying treatment. The group consisted of 30 individuals who were administered a depot analogue preparation at 4 weekly intervals (12 received Goserelin monthly, three received Decapeptyl monthly). At the end of the 12 week pretreatment period they were admitted for myomectomy. These were compared with a group of 15 controls undergoing myomectomy to whom no pretreatment was given. The controls were matched such that the uterine size in the control patients was equivalent to the size of the uterus following 3 month pretreatment with GnRH analogue. The reason for this was to try and avoid the bias in the study in which the post-treatment size uteri of patients pretreated with GnRH analogue would inevitably be smaller than it was pretreatment if matched for size at onset.

During surgery, all performed by one surgeon using the same technique with no tourniquets nor injection of any vasoconstrictor agents, blood loss was accurately measured using the alkaline haematein dilution technique (Hallberg and Nilsson, 1964). Blood was collected and swabs retained following opening of the peritoneal cavity until completion of surgery and closure of the abdominal peritoneum. Table IV indicates that the pretreatment group had significantly less blood loss during myomectomy than controls and that fewer patients required blood transfusion in those who had been pretreated with a GnRH analogue compared with those who had not.

Conclusions

GnRH analogues prior to myomectomy offer patients clear advantages which can be summarized as follows: (i) correction of any pre-operative anaemia associated with the control of any concomitant menorrhagia; (ii) pretreatment with GnRH analogue increases uterine artery resistance index (RI) values as measured by Doppler ultrasound and indicates reduced uterine artery blood flow; (iii) this is associated with a reduced intra-operative blood loss at myomectomy when compared with controls untreated and matched for uterine size; (iv) the
optimum duration of pretreatment is 2–3 months. It is important that surgery is performed during a continuing state of hypo-oestrogenaemia and pituitary down-regulation. Continuation of this state into the post-operative phase may have additional advantages of preventing post-operative venous oozing, haematoma and adhesion formation; however, definitive studies to substantiate these claims have not been reported in the literature as yet.

References


