Polycystic ovary syndrome. A therapeutic challenge

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CHAPTER 3

Pulsatile gonadotrophin releasing hormone for ovulation induction in subfertility associated with polycystic ovary syndrome

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Abstract

Background
In normal menstrual cycles, gonadotrophin releasing hormone (GnRH) secretion is pulsatile, with intervals of 60-120 minutes in the follicular phase. Treatment with pulsatile GnRH infusion by the intravenous or subcutaneous route using a portable pump has been used successfully in patients with hypogonadotrophic hypogonadism. Assuming that the results would be similar in women with polycystic ovary syndrome (PCOS), pulsatile GnRH has been used to induce ovulation in these women. Although ovulation and pregnancy have been achieved, the effectiveness of pulsatile GnRH in women with PCOS has not been clearly demonstrated.

Objectives
To assess the effectiveness of pulsatile GnRH administration in women with polycystic ovary syndrome (PCOS), in terms of ongoing pregnancy, ovulation, clinical pregnancy, ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, miscarriage, and multifollicular growth.

Search strategy
We searched the Cochrane Menstrual Disorders & Subfertility Group trials register (searched 13 August 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 2, August 2001), MEDLINE (January 1966 to August 2003), EMBASE (January 1985 to August 2003) and reference lists of articles. We also contacted manufacturers and researchers in the field.

Selection criteria
All relevant published randomised clinical trials were selected for inclusion if treatment consisted of pulsatile GnRH administration versus another treatment for ovulation induction in subfertile women with PCOS.

Data collection & analysis
Relevant data were extracted independently by two reviewers (NB, MW). Validity was assessed in terms of method of randomisation, completeness of follow-up, presence or absence of crossover and co-intervention. All trials were screened and analysed for predetermined quality criteria. Data synthesis: 2X2 tables were generated for all the relevant outcomes. Odds ratios were generated using the Peto method.

Main results
Four randomised clinical trials involving 57 women were identified comparing four different treatments: GnRH versus HMG, GnRH and FSH versus FSH, GnRH following pretreatment with GnRH agonist (GnRHa) versus GnRH only, GnRH following pretreatment with GnRHa versus clomiphene citrate. This means that there was only one trial in any one comparison. In two studies, data of pre- and post-crossover were not described separately. All trials were small and of too short duration to show any significant differences in pregnancy results. The odds ratio for ongoing pregnancy, only described in one trial, was 7.5 (95% CI 0.44 to 127) in the comparison GnRH following pretreatment with GnRHa versus GnRH only in favour of the first group. Multiple
pregnancies were not seen. Ovarian hyperstimulation syndrome was seen only in women allocated to ovulation induction with HMG.

**Reviewers' conclusions**

The four trials describing four different comparisons with a short follow up (1 to 3 cycles) were too small to either prove or discard the value of pulsatile GnRH treatment in patients with polycystic ovary syndrome.
Background

Induction of ovulation in patients with polycystic ovarian syndrome still presents a clinical challenge. The first effective treatment to restore ovulation in patients with PCOS was bilateral ovarian wedge resection (BOWR), advocated by Stein and Leventhal in 1935 (Stein and Leventhal, 1935). This mode of treatment led to mechanical sterility which dramatically dampened enthusiasm for this surgical approach. In 1961, Greenblatt reported successful induction of ovulation in amenorrhoeic women with clomiphene citrate (Greenblatt et al., 1961). However, about 20% of patients with PCOS are resistant to clomiphene citrate (Imani et al., 1998). In 1962, the first pregnancies with urinary derived human menopausal gonadotrophins were reported (Lunenfeld et al., 1962). However, ovulation induction with urinary gonadotrophins in patients with PCOS bears the risk of hyperstimulation (multiple follicular development leading to cycle cancellation), ovarian hyperstimulation syndrome (OHSS), and multiple pregnancy (Nugent et al., 2003).

Inspired by the positive effects of treatment with pulsatile GnRH in women with hypogonadotropic amenorrhoea, Coelingh Bennink (Coelingh Bennink, 1983) was the first to select 11 women with PCOS in whom all other methods of ovulation induction had failed, for this treatment. Since then it has been used as a treatment modality to induce ovulation in clomiphene citrate resistant women with PCOS as well as a first line treatment in these women. The theoretical advantage would be that the intact negative feedback of steroids during GnRH therapy should - in contrast to hMG/hCG therapy - lead to monofollicular growth, thereby minimizing the chance of ovarian hyperstimulation syndrome and multiple pregnancy. Although ovulation and pregnancies were achieved, the use of pulsatile GnRH in women with PCOS did not lead to the same success rates as achieved in hypogonadotropic amenorrhoea. To improve clinical outcome in women with PCOS, suppression of endogenous gonadotrophins through pretreatment with GnRH agonists (GnRHa), thereby creating a temporary endocrine milieu similar to hypogonadotropic hypogonadism, was the next logical concept.

Objectives

To determine the effectiveness of pulsatile GnRH administration by the intravenous or subcutaneous route with a portable pump to induce ovulation in women with polycystic ovary syndrome.

Criteria for considering studies for this review

Types of studies
A randomised clinical trial was eligible for inclusion if it dealt with the use of GnRH for ovulation induction in PCOS. Four randomised trials were found. Non-randomised controlled trials were excluded.
Types of participants
Subfertile patients with anovulation and PCOS. Description of PCOS, endocrinological and clinical characteristics, infertility work-up, age, duration of infertility and previous treatment(s) are specified in the trial characteristics table, if available.

Types of interventions

* **GnRH versus other forms of ovulation induction**
  * GnRH versus gonadotrophins

* **GnRH combined with other forms of ovulation induction versus GnRH and/or other forms of ovulation induction**
  * GnRH + gonadotrophins versus gonadotrophins
  * GnRH + clomiphene citrate versus GnRH

* **GnRH combined with GnRH agonist versus GnRH and/or other forms of ovulation induction**
  * GnRH + GnRHa versus GnRH
  * GnRH + GnRHa versus GnRH + oral contraceptive

* **Different modalities of GnRH administration**
  * Intravenous versus subcutaneous GnRH administration

Types of outcome measures

* **Primary Outcome**
  * Ongoing pregnancy or live birth rate per woman

* **Secondary Outcomes**
  * Clinical pregnancy rate (per woman)
  * Ovulation rate (per woman)
  * Incidence of OHSS (per woman)
  * Incidence of multiple pregnancy (per woman)
  * Miscarriage rate (per woman)
  * Incidence of multifollicular growth (per woman)

Search strategy for identification of studies

We searched the Cochrane Menstrual Disorders & Subfertility Group trials register (searched 13 August 2003), the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 2, August 2001), MEDLINE (January 1966 to August 2003), EMBASE (January 1985 to August 2003) and reference lists of articles. We also contacted manufacturers and researchers in the field. The Cochrane Menstrual Disorders and Subfertility Group register is based on regular searches of MEDLINE, EMBASE, CINAHL, PsycINFO and CENTRAL, the handsearching of 20 relevant journals and conference proceedings, and searches of several key grey literature sources.
A full description is given in the Group's module on the Cochrane Library. One randomised clinical trial (Bringer et al., 1985) and one abstract (Coelingh Bennink, 1983) were identified by looking at reference lists of trials identified by the search.

**Methods of the review**

**Selection of studies & quality assessment**
Data from included trials was processed as described in the Cochrane Handbook (Clarke and Oxman, 2003). All selected studies were assessed and evaluated for methodological quality and appropriateness for inclusion without consideration of their results. Trials were screened and analysed for the following quality criteria: method and timing of randomisation; the number of patients randomised and analysed; whether they were single or multicenter studies; single phase or cross-over design; blinding of treatment; the use of sequential analysis or factorial design; the presence of a power calculation; duration of follow-up; whether pregnancy was a measured outcome and, if so, how this was diagnosed; how pregnancy results were presented (particularly whether cumulative conception curves with the use of life table analysis were employed); and the source of any funding. Relevant trials were screened independently by two authors (NB and MW). Differences of opinion were registered and resolved by consensus with the senior author (FV). When crossover studies were identified, only the first phase data, if available, were included in the results. In this review no pooling of data has been conducted and therefore the current overview presents Peto odds ratios only (Peto, 1987).

**Description of studies**

*Please see Appendix II for features of the four trials included in the analysis.*

**Types of studies**
Four randomised studies (Bringer et al., 1985; Remorgida et al., 1991; Scheele et al., 1993; Timmerman et al., 2000) were identified. The first three randomised studies were crossover studies. In the study of Bringer (1985) patients were crossed over after three treatment cycles. In the other two, patients who did not conceive were crossed over after one treatment cycle (Remorgida et al., 1991; Scheele et al., 1993). In the study of Bringer (1985) and Scheele (1993) data of pre- and post- crossover were not described separately and were therefore not included in the analysis. The total number of women included was 57.

**Types of participants**
PCOS was defined as a combination of clinical features, endocrinological abnormalities, and ovarian appearance on ultrasound and diagnostic laparoscopy in one trial (Bringer 1985) and a combination of the first two criteria in the other three trials (Remorgida et al., 1991; Scheele et al., 1993; Timmerman et al., 2000). In two studies the included patients had previously failed to ovulate on treatment with clomiphene citrate (Bringer et al., 1985; Remorgida et al., 1991). The other trials did not select for clomiphene citrate resistance. In the trial by Remorgida (1991) all patients had undergone prior ovulation
induction with GnRH. Data on age, body mass index and LH/FSH ratio could be extracted from all except one study (Bringer et al., 1985). The duration of pre-existent infertility was only stated in two trials (Remorgida et al., 1991; Timmerman et al., 2000).

**Types of intervention**

**Types of outcome**
Pregnancy rate (per cycle/per woman) and ovulation rate (per cycle) were the main outcome measures of interest in all of the studies. The diagnosis of pregnancy and ovulation was only defined in one study (Timmerman et al., 2000). In the study by Scheele (1993) “ongoing pregnancies” were reported without a definition of this primary outcome. Although without a definition of ongoing pregnancy, we decided to analyse these pregnancies as ongoing. Because of no definition of pregnancy in two trials (Bringer et al., 1985; Remorgida et al., 1991) and pregnancy defined as determination of B-hCG in the urine and serum in the study by Timmerman (2000), we decided to analyse these pregnancies as clinical pregnancy.

The other primary outcome i.e. live birth rate (per woman) was not reported by any of the studies. The main adverse outcomes were multifollicular growth, multiple pregnancy, OHSS and miscarriage. None of these outcomes were defined in the four included studies.

**Methodological quality of included studies**
Overall, the quality of the included trials was poor. The method of allocation was by using sealed envelopes in the study of Timmerman (2000) (oral communication). The allocation procedure was unknown for the other trials. There was no blinding, and power calculations and intention to treat analyses were not performed. All studies were conducted in a single centre. In general, the sample size of the studies was small (range 8 to 28) and the follow-up was short (1 to 3 cycles). No definitions on the outcome parameters were given. Cumulative conception curves or life table analysis were not employed.

We expect the study of Bringer (1985) was supported by Ferring as this study was published in a Ferring publication only.
Results

As each of the four included trials described a different comparison, no trial results could be combined. Analyses are presented separately for each comparison.

**Pulsatile GnRH versus HMG (Bringer et al., 1985)**

As data from the first phase of the crossover study could not be obtained this study was not included in the MetaView analysis. The primary outcome i.e. live birth rate (per woman) was not reported. Ongoing pregnancy rate could not be extracted from this trial. Only clinical pregnancy was expressed per woman, the other outcome parameters were described per cycle. Two clinical pregnancies occurred in both treatment groups. Ovulation occurred in 5 of 18 cycles (28%) following pulsatile GnRH and in 10 of 17 cycles (59%) after ovulation induction with FSH. Incidence of miscarriage and multiple pregnancies could not be extracted from this study. OHSS occurred in one of 18 cycles in women treated with pulsatile GnRH and in six of 17 cycles in women following ovulation induction with HMG.

**Pulsatile GnRH and FSH versus FSH only (Remorgida et al., 1991)**

The primary outcome i.e. live birth rate (per woman) was not reported. Ongoing pregnancy rate could not be extracted from this trial. One of four women (25%) treated with pulsatile GnRH and FSH and none of four women treated with FSH only got pregnant resulting in an odds ratio of 7.4 (95% CI 0.15 to 372). The ovulation rate per woman was significantly higher in the pulsatile GnRH and FSH group (4 of 4) compared to the FSH group (1 of 4). The odds ratio was 16.4 (95% CI 1.13 to 239). However, as this study was performed with 8 patients only, its clinical significance is limited. Incidence of miscarriage and multiple pregnancy could not be extracted from this study. Multifollicular growth was observed in the FSH group only (three of four women) and resulted in cancellation of these cycles.

**Pulsatile GnRH following pretreatment with GnRHa versus GnRH only (Scheele et al., 1993)**

As data from the first phase of the crossover study could not be obtained this study was not included in the MetaView analysis. The primary outcome i.e. live birth rate (per woman) was not reported. Only ongoing and clinical pregnancy were expressed per woman, the other outcome parameters were described per cycle. In this trial with 12 patients two ongoing pregnancies were found in the GnRH following pretreatment with GnRHa group (17%) and none in the GnRH group only. Treatment with GnRH following pretreatment with GnRHa resulted in two clinical pregnancies and in one clinical pregnancy with no GnRHa pretreatment. Ovulation occurred in 10 of 12 cycles (83%) in women treated with GnRH following pretreatment with GnRHa and 8 of 11 cycles (73%) without pretreatment with GnRHa. Only one miscarriage occurred in a woman treated with GnRH without pretreatment with GnRHa. Multifollicular growth was observed in both treatment arms; four of 12 cycles (33%) in women treated with pulsatile GnRH following pretreatment with GnRHa and in two of 11 cycles (18%) in women with no GnRHa pretreatment.
**Pulsatile GnRH following pretreatment with GnRHa versus clomiphene citrate (Timmerman et al., 2000)**

The primary outcome i.e. live birth rate (per woman) was not reported. Ongoing pregnancy rate could not be extracted from this trial. Only clinical pregnancy was expressed per woman. For ovulation and multifollicular growth only data per cycle was available. Clinical pregnancy occurred in four of 16 women (25%) treated with pulsatile GnRH following pretreatment with GnRHa and four of 12 women (33%) treated with clomiphene citrate. The odds ratio was 0.67 (95% CI 0.13 to 3.4). Ovulation occurred in 19 of 40 cycles (46%) in women treated with pulsatile GnRH following pretreatment with GnRHa and in 15 of 25 cycles (60%) in women treated with clomiphene citrate. Multifollicular growth was observed in four of 25 cycles in women treated with clomiphene citrate. No incidence of OHSS or miscarriage was observed.

**Discussion**

The randomised clinical trials included in this review describe four different comparisons: pulsatile GnRH versus hMG (Bringer et al., 1985), pulsatile GnRH and FSH versus FSH (Remorgida et al., 1991), pulsatile GnRH following pretreatment with GnRHa versus pulsatile GnRH (Scheele et al., 1993) and pulsatile GnRH following pre-treatment with GnRHa versus clomiphene citrate (Timmerman et al., 2000). In the last two studies, pulsatile GnRH was used as a first line treatment in patients who were not resistant for clomiphene citrate. At this moment however, clomiphene citrate is because of its efficacy, safety and ease of use, usually the drug of first choice for ovulation induction in women with PCOS. Treatment with clomiphene citrate leads to an ovulation rate of approximately 80% and a cumulative pregnancy rate of 73% after nine ovulatory cycles (Imani et al., 1998; Imani et al., 1999). The comparisons in these two studies (Scheele et al., 1993; Timmerman et al., 2000) are therefore of no clinical significance.

The comparison of pulsatile GnRH and FSH versus FSH alone is also of no clinical significance as it was designed to verify whether the risk of premature luteinization could be avoided by combining pulsatile GnRH and gonadotrophins. The comparison of pulsatile GnRH versus hMG (Bringer et al., 1985) in clomiphene citrate resistant patients with PCOS is the only one of interest for this review. However, because of the crossover design and the very small number of patients, no conclusions can be drawn on efficacy and safety of GnRH compared to hMG.

Summarizing, the randomised clinical trials comparing pulsatile GnRH with other forms of ovulation induction are few and those that have been published were trials with a very small numbers of patients, with low quality and in three studies even irrelevant comparisons were performed. The only one with a clinically relevant comparison (Bringer et al., 1985) was too small and had a crossover design, because of which no conclusions can be drawn on the effectiveness and safety of treatment with pulsatile GnRH in women with clomiphene citrate resistant patients with PCOS. This is unfortunate, as the clinical problem is posed by patients with clomiphene citrate resistant PCOS.

Therefore, we collected all uncontrolled case-series on pulsatile GnRH. Studies were excluded from this case-series when other forms of ovulation induction like
gonadotrophins or wedge resection had been used before ovulation induction with pulsatile GnRH.

We found 11 studies that treated a total of 179 clomiphene citrate resistant women with PCOS (Burger et al., 1983; Ross et al., 1985; Burger et al., 1986; Jansen et al., 1987; Eshel et al., 1988; Wilson et al., 1988; Bolanowski et al., 1989; Rossmanith et al., 1989; Surrey et al., 1989; Saffan and Seibel, 1992; Tan et al., 1996). The ovulation rate in these studies ranged from 0 to 100% per cycle, the pregnancy rate per patient was 17% (range 0-50%) and a 20 to 67% miscarriage rate was reported in three studies. One quadruplet was described (Saffan and Seibel 1992) and none of the patients developed an OHSS.

We found three studies that treated a total of 69 non clomiphene citrate resistant women with PCOS (Ficiori et al., 1988; Ficiori et al., 1991; Mais et al., 1991). The ovulation rate per cycle in these studies ranged from 43 to 83%, the pregnancy rate per patient was 15% (range 10-17%) and a 0 to 100% miscarriage rate was reported. One multiple pregnancy was recorded (Ficiori et al., 1991) and none of the patients developed an OHSS.

We found three studies that treated a total of 73 non clomiphene citrate resistant women with PCOS with pulsatile GnRH following pre-treatment with GnRHa (Ficiori et al., 1988; Ficiori et al., 1991; Ficiori et al., 1994). The total ovulation rate per cycle was 78% (range 76-100), the pregnancy rate per patient was 34% (range 5-67) and a 0 to 50% of miscarriage was reported in two studies. No multiple pregnancy was described and none of the patients developed an OHSS.

We found only one study that treated a total of 9 clomiphene citrate resistant women with PCOS with pulsatile GnRH following pre-treatment with GnRHa (Surrey et al., 1989). Ovulation rate per cycle was 29% and no pregnancies occurred.

Overall, the data do suggest that pulsatile GnRH may be useful in women who are resistant to clomiphene citrate, although much less so than in women with hypogonadotropic hypogonadism. Whether pretreatment with GnRHa increases the effectiveness of pulsatile GnRH in these women cannot be deducted from the available data.

Recent evidence from a meta-analysis suggests that metformin increases the effectiveness of ovulation induction with clomiphene in terms of ovulation and pregnancy rate and should therefore also be used as a first line agent for ovulation induction in women with PCOS (Lord et al., 2003). Women not responding to clomiphene, whether co-treated with metformin or not, generally undergo ovulation induction with FSH or a surgical procedure like laparoscopic electrocautery of both ovaries. Ovulation induction with urinary FSH and recombinant FSH was found to result in a pregnancy rate of 38% and 40% per woman respectively (Bayram et al., 2003). Ongoing pregnancy rate per woman was 52% after electrocautery of the ovaries compared to 50% with gonadotrophins (Farquhar et al., 2003). Although a significant difference in pregnancy rate or pregnancy outcome between electrocautery of the ovaries and gonadotrophins was not demonstrated no cases of OHSS and more importantly, no multiple pregnancies were observed after
electrocautery of the ovaries. Therefore, laparoscopic electrocautery of the ovaries may be the treatment of choice since the avoidance of gonadotrophins may reduce the risk of OHSS and multiple pregnancy. Similar to laparoscopic electrocautery the theoretical advantages of pulsatile GnRH are minimization of the chances of ovarian hyperstimulation syndrome and multiple pregnancy and therefore treatment with GnRH is still a point of interest. However, because of insufficient evidence from randomised clinical trials and the very scarce data amongst women with clomiphene citrate resistant PCOS from uncontrolled case-series with a clinically appropriate treatment i.e. GnRH following pretreatment with GnRHa, the relevance of GnRH remains unclear.

More large randomised trials are needed to assess the value of GnRH in ovulation induction in patients with clomiphene citrate resistant PCOS.

**Reviewers' conclusions**

**Implications for practice**  
Considering the limited number of randomised clinical trials, and the fact that those that have been published are small, of short duration and of low quality, no conclusions can be drawn on the use and relative effectiveness of pulsatile GnRH in women with clomiphene citrate resistant PCOS.

**Implications for research**  
Theoretically, treatment with pulsatile GnRH can minimize complications. Large randomised trials are needed to assess the value of GnRH in ovulation induction in women with PCOS not responding to clomiphene citrate or a combination of clomiphene citrate and metformin. Valuable randomised clinical trials are trials that:
1. compare pulsatile GnRH with or without pretreatment with GnRHa and ovulation induction with FSH with live births and occurrence of multiple pregnancies as main outcomes.
2. compare pulsatile GnRH with or without pretreatment with GnRHa and laparoscopic electrocautery of the ovaries with live birth as primary outcome.

**References**

**References to included studies**


References to excluded studies


Additional references


Characteristics of excluded studies

Gerhard et al., 1993: Non-randomized controlled study

Homburg et al., 1990: Non-randomized controlled study and great part of the patients were previously treated with GnRH.