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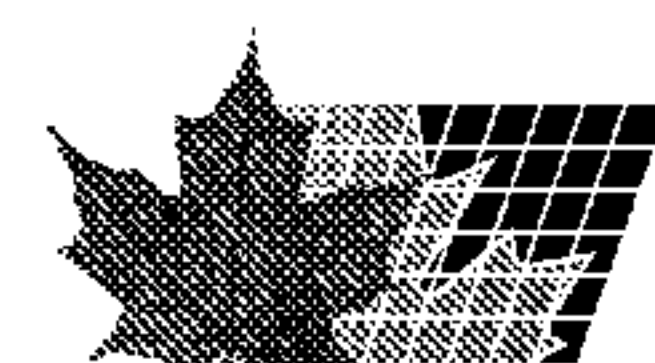
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(54) Titre : COMPOSITION POUR DIAGNOSTIC  
(54) Title: DIAGNOSTIC COMPOSITION

(57) **Abrégé/Abstract:**

The invention relates to a diagnostic composition for improving the effectiveness of hysteroscopy, characterized in that it contains an LH-RH antagonist, in particular cetrorelix. The composition is envisaged for use prior to hysteroscopy and/or for preparation for surgery, specifically in a single dose of between 0.1 and 2 mg/kg. However, the composition can also be administered, for use prior to hysteroscopy and/or for preparation for surgery, in a multiple dose of between 0.01 and 0.5 mg/kg, preferably spread over 1-14 days. The composition is furthermore suitable for use in hysteroscopy in combination with the subsequent treatment of pathological conditions of the uterus such as myoma and endometrial hyperplasia.



**Abstract:**

The invention relates to a diagnostic composition for improving the effectiveness of hysteroscopy, characterized in that it contains an LH-RH antagonist, in particular cetrorelix. The composition is envisaged for use prior to hysteroscopy and/or for preparation for surgery, specifically in a single dose of between 0.1 and 2 mg/kg.

However, the composition can also be administered, for use prior to hysteroscopy and/or for preparation for surgery, in a multiple dose of between 0.01 and 0.5 mg/kg, preferably spread over 1-14 days. The composition is furthermore suitable for use in hysteroscopy in combination with the subsequent treatment of pathological conditions of the uterus such as myoma and endometrial hyperplasia.

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**Diagnostic composition**

The invention relates to a diagnostic composition to be used, in particular, in preparing for hysteroscopy.

5 Hysteroscopy is to be understood as being the endoscopic inspection of the uterine cavity using a special endoscope (hysteroscope). Hysteroscopy is an essential diagnostic method for assessing various uterine diseases, for example myomas and endometrial  
10 hyperplasia.

It is known from Gynaecol.-Endoscopy 4:4 259-264 1995 to employ GnRH analogues, in this case triptorelin, prior to laparoscopic myomectomy. Furthermore,  
15 endometrial hyperplasia has been treated with the LH-RH agonist triptorelin in association with hysteroscopic and diagnostic curettage (Contraception-Fertilite-Sexualite 23, 9, 516-523, (1995)). It is known from J. Gynaecol. Surg., 11:2, 65-70 (1995) to assess the  
20 effect of endometrial thinning with Gn-RH agonists (Zoladex) with regard to the results of hysteroscopic, endometrial electrosurgical resection. It is recommended that the endometrium be prepared prior to hysteroscopic surgery.

25 Results obtained in association with the treatment of infertility with GnRH analogues are known from TW. Gynaecol. 6:6,382-390 (1993), according to which [lacuna] the volume of leiomyomas is effected prior to laparoscopic myomectomy or hysteroscopic resection.

30 It has not previously been known to use LHRH antagonists, in particular cetrorelix, in connection with hysteroscopic diagnosis or preparation for surgery.

35 An object of the invention is therefore to provide a composition for improving the results of hysteroscopy carried out in connection with the diagnosis of uterine conditions, in particular in association with

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endometrial hyperplasia, leiomyomas or malignant diseases. The invention additionally makes it possible to carry out non-invasive therapy or an operation without any long preparation time. This can  
5 simultaneously be combined with a treatment of the abovementioned diseases.

The object is achieved by employing LH-RH antagonists, in particular the LH-RH antagonist cetrorelix, which is  
10 known, for example, from EP 0 299 402, in preparing for hysteroscopy in association with the abovementioned applications.

Because the effect of cetrorelix begins immediately,  
15 the use of this compound is also particularly indicated in connection with the diagnosis and therapy of myoma bleeding, for example.

Diagnosis can advantageously move on directly into  
20 therapy using therapeutic doses.

Leiomyomas, for example, can be treated in accordance with the following scheme:

#### Example

25

In one embodiment of the invention, from 0.1 to 2 mg of cetrorelix per kg of body weight are injected as a single dose or in amounts of from 0.01 to 0.5 mg per kg of body weight which are spread out over 1 to 14 days.

30

This results in a decrease in the thickness of the endometrial layer and, consequentially, in the possibility of more effective hysteroscopic assessment and therapy of pathological conditions. Due to the fact that the effect of cetrorelix begins rapidly,  
35 administration of this compound is also particularly indicated in association with the diagnostic preparation for operations, such as for mammary carcinomas, which cannot be delayed.

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Table 1 below shows the decrease, or the stagnation, in endometrial growth as monitored in a female patient having the initials 112 KB, and is explained in that which follows:

5

Cetrorelix pamoate: provisional results of the clinical experiments:

10 Treatment of a female patient with uterine fibrosis, which was operated on.

Injection of 60 mg of cetrorelix on days 2 and 28 of the menstrual cycle.

15 The endometrium was measured by ultrasonics and did not exhibit any growth during the treatment with cetrorelix. Hysteroscopic and laparoscopic myoma resection was carried out with ease and without any significant blood loss only 2 months after beginning the cetrorelix therapy.

20 Due to the fact that the thickness of the endometrial layer begins to decrease immediately after injecting cetrorelix, a short period, of from 7 to 14 days, of treatment with cetrorelix is sufficient for diagnostic investigations or for ablation of the endometrium.

Table 1

| Patient | Dose                                      | Date     | Treatment days             | Time  | Endometrium [mm] | E2 pg/ml | Comments                                                        |
|---------|-------------------------------------------|----------|----------------------------|-------|------------------|----------|-----------------------------------------------------------------|
| 11 KB   |                                           | 26.02.96 | screening                  |       | flat/even        |          |                                                                 |
| "       | 1st injection 60 mg of cetrorelix pamoate | 03.03.96 | Day 0                      | 10:15 |                  | 25       |                                                                 |
| "       |                                           | 11.03.96 | Day 7                      | 16:40 | 2                | <5       |                                                                 |
| "       |                                           | 08.03.96 | Day 14                     | 17:30 | flat/even        | 17       |                                                                 |
| "       |                                           | 25.03.96 | Day 21                     | -     | 3.1              | 40       |                                                                 |
| "       | 2nd injection 60 mg of cetrorelix pamoate | 01.04.96 | Day 28                     | 18:00 | flat/even        | 88       |                                                                 |
| "       |                                           | 15.04.96 | Day 42                     | 17:00 | flat/even        | 25       |                                                                 |
| "       |                                           | 29.04.96 | Day 55<br>End of the study | 16:15 | flat/even        | 73       |                                                                 |
| "       |                                           | 07.05.96 | Day of operation           | 14:00 |                  | 114      | laparoscopic myoma enucleation<br>hysteroscopic myoma resection |

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Explanation of enclosed Figures 1 to 3:

Figure 1 shows a surgical photograph before beginning hysteroscopic myoma ablation

5 Figure 2 shows a surgical photograph following hysteroscopic myoma ablation.

Ostium pubae internum at the top on the left

Figure 3 shows the enucleation of the subserosal fundus myoma

10

The principal advantages of the invention are:

→ improved diagnostic principle based on rapid hormone suppression and consequently rapid reduction or interruption of the endometrial volume and consequently  
15 improvement in hysteroscopic diagnosis and shorter period of treatment as compared with known methods

→ very good tolerability due to the absence of initial stimulation (flare up).

20

Particular advantages of premedication with cetorelix are:

→ it is possible to begin treatment irrespective of menstrual cycle status

25 → short treatment period of from 7 to 10 days and therefore no side effects and no, or only trivial, symptoms of hormone deficiency

→ good timing for the hysteroscopic inspection

30 Comparison with existing therapies

→ LHRH agonists: initial flare up

a) long period of treatment (4 weeks)

b) greater frequency of hormone deficiency symptoms

c) increase in bleeding during the first few days

35

→ Gestagens:

irregular bleeding

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→ Danazol:

- a) high doses are required
- b) long period of treatment (4-6 weeks)
- c) side effects: acne, hirsutism and increase in weight

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A diagnostic composition for improving the effectiveness of hysteroscopy, comprising a luteinizing hormone-releasing hormone (LH-RH) antagonist together with a pharmaceutically acceptable diluent or carrier.
2. A composition according to claim 1, wherein the LH-RH antagonist is cetrorelix.
3. A composition according to claims 1 or 2, for use prior to hysteroscopy or for preparation for surgery, and which is formulated for administration of the LH-RH antagonist in a single dose of between 0.1 and 2 mg/kg of body weight.
4. A composition according to claims 1 or 2, for use prior to hysteroscopy or for preparation for surgery, and which is formulated for administration of the LH-RH antagonist in multiple doses of between 0.01 and 0.5 mg/kg of body weight.
5. A composition according to claim 4, wherein the multiple doses are spread over 1 to 14 days.
6. A composition comprising cetrorelix together with a pharmaceutically acceptable diluent or carrier, for use in improving the results of hysteroscopy in combination with

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subsequent endometriosis treatment, or ablation of a myoma or an endometrial hyperplasia.

7. Use of a luteinizing hormone-releasing hormone (LH-RH) antagonist in the manufacture of a diagnostic composition for improving the effectiveness of hysteroscopy.

8. Use according to claim 7, wherein the LH-RH antagonist is cetrorelix.

9. Use according to claim 7 or 8, wherein the composition is formulated for administration of the LH-RH antagonist in a single dose of between 0.1 and 2 mg/kg of body weight for use prior to hysteroscopy or for preparation for surgery.

10. Use according to claim 7 or 8, wherein the composition is formulated for administration of the LH-RH antagonist in multiple doses of between 0.01 and 0.5 mg/kg of body weight for use prior to hysteroscopy or for preparation for surgery.

11. Use according to claim 10, wherein the multiple doses are spread over 1 to 14 days.

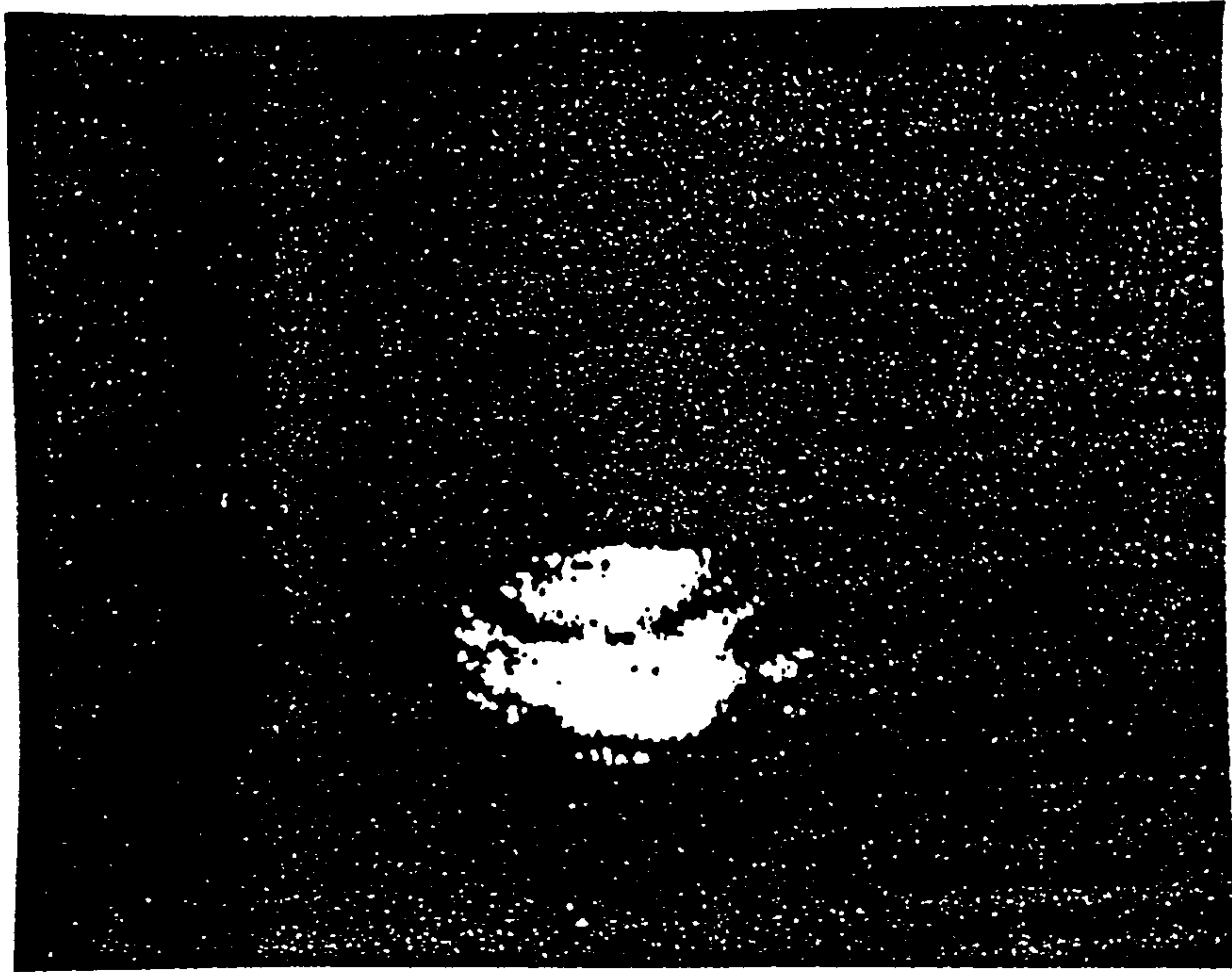
12. Use of cetrorelix in the manufacture of a composition for use in improving the results of hysteroscopy in combination with subsequent endometriosis treatment, or ablation of a myoma or an endometrial hyperplasia.

Figure 1



Marks of Olerk

Figure 2



Mark & Clerk

Figure 3



Mark A. Clark