Ultrasonic measurement of ovarian follicles, ovarian and uterine size during induction of ovulation with human gonadotrophins

Pekka Ylöstalo¹, Per Gunnar Lindgren² and Sven Johan Nillius³

Department of Obstetrics and Gynaecology¹, University of Oulu, Oulu, Finland, Department of Diagnostic Radiology² and Obstetrics and Gynaecology³, University Hospital, Uppsala, Sweden

Abstract. Twelve anovulatory women were examined by compound B-mode and real-time ultrasound scanning during induction of follicular maturation and ovulation, by human gonadotrophins. The treatment was monitored by daily serum oestrogen determinations. Ovarian follicles became visible on the ultrasound scans after 4 days of treatment, on average. The mean follicular diameter at that time was 8 mm. Multiple follicles developed in all but one of the 12 patients. At induction of ovulation the diameter of the dominant follicle varied between 15 and 22 mm. The serum oestrogen level was related to the number of follicles, the diameter of the greatest follicle and the ovarian size. There was a marked increase in the ovarian size during the treatment. The size of the uterus also increased. Ultrasound may be a valuable complement to daily oestrogen determinations for monitoring human gonadotrophin therapy.

Visualization of the ovaries by ultrasound was described by Kratochwil et al. (1972). Studies during recent years have shown that ultrasound can be used to define and measure ovarian follicles with a diameter of 10 mm and above. This has been demonstrated by compound B-mode scanning (Hackelöer et al. 1977; Hackelöer & Robinson 1978) and recently also by real-time scanning (O’Herlihy et al. 1980a).

During the normal menstrual cycle, the dominant follicle can be observed by ultrasound 4–5 days before ovulation. The follicular diameter increases 1–4 mm per day and ranges between 13 and 27 mm on the day of presumptive ovulation (Hackelöer et al. 1979; Ylöstalo et al. 1979; O’Herlihy et al. 1980a,b; Renaud et al. 1980). Assessment of ovulation by ultrasound and serum oestradiol has been utilized for timing of artificial insemination (Rönnberg et al. 1978; Robertson et al. 1979; Saint-Pol et al. 1980). Reports on the use of ultrasonic monitoring of ovarian follicular growth during induction of ovulation by domiphen or human gonadotrophins have recently appeared (Ylöstalo et al. 1979; Nitschke-Dabelstein et al. 1980; Queenan et al. 1980; Smith et al. 1980).

Here we describe changes in the ovaries and uterus observed by ultrasonic compound B-mode and real-time scanning during human gonadotrophin treatment of anovulatory women.

Patients and Methods

Twelve women with anovulatory infertility were studied with ultrasound during a treatment course with human gonadotrophins. Human menopausal gonadotrophin (hMG, Humegon®, Organon) was administered daily as an im injection using an individually adjusted treatment schedule. The patients were examined daily during the treatment and basal body temperature, cervical mucus quality and findings on pelvic examination were recorded. The ovarian response was evaluated by daily estimation of the serum oestrogen level. Daily venous blood samples were taken in the morning and assayed for immunoreactive oestrogens by a radioimmunological technique using a sheep anti-oestradiol-6-oxime BSA antiserum (Lindberg et al. 1974). hMG treatment was continued until the serum oestrogen concentration reached a level of 2000–3000 pmol/l. Ovulation was then
induced by a single im injection of 6000–9000 IU of human chorionic gonadotrophin (hCG, Pregnyl®, Organon).

Ultrasound examinations were performed every day or every second day during the treatment with hMG, at induction of ovulation with hCG and one week later. The ultrasonic equipment was a real-time scanner Toshiba Sonolayer L with a transducer of 3.5 MHz and a gray scale compound scanner Philips Sonodiagnost B50 with a transducer of 3.5 MHz LIF (long internal focus). The patients were mostly examined with both scanners each day. An exacting technique with full bladder (Hackelöer et al. 1977; Ylöstralo et al. 1979) was used. Both longitudinal and transverse scannings were performed every 0.5 cm. The ultrasound velocity was calibrated to 1540 ms.

The ultrasonic findings were photographed on Polaroid film. The measurements of the size of ovarian follicles, ovaries and uterus were made either from the photographs utilizing the measuring scale of the apparatus or during the ultrasonic examination applying the marker-digital display of the apparatus. The diameter of the ovarian follicles was measured. If the follicle was not completely circular, the mean value of the longest and shortest diameter was used. The equation for the measurement of an oval area was used for estimation of the size of the ovaries and the uterus. The area of the image of the ovaries and uterus was measured on the longitudinal ultrasound scan obtained with the compound scanner.

Results

The ovarian follicle(s) first became visible on the ultrasound scan 2–7 days (mean 4.3) after initiation of the hMG treatment. The mean diameter of the follicle at that time was 8.4 mm (range 6–12). The results were similar with the real-time and compound scanner. The daily growth of the dominant follicle was 2.8 ± 0.3 mm (mean ± SEM) and ranged from 0 to 8 mm, being greatest immediately before induction of ovulation. As a rule, more than one follicle began to grow (Fig. 1).

![Fig. 1.](image)

Transverse ultrasonic scan (compound scanner) after 8 days of daily treatment with 150 IU of human menopausal gonadotrophins in a 26-year-old women (OK) with one year of secondary amenorrhoea. Both ovaries and the uterus are seen behind the bladder. Four follicles (diameter 16, 13, 10 and 10 mm) are visible in the left ovary and two follicles (12 and 12 mm) in the right ovary. The serum oestradiol level at the day of examination was 3700 pmol/l and the serum progesterone level 0.36 nmol/l. 9000 IU of hCG was administered and ovulation with normal corpus luteum function occurred.
Multiple follicles in the ovaries were found in all but one of the 12 patients at the time of the ovulation-inducing hCG injection. The mean number of follicles observed at that time with the real time scanner was 3.1 (range 1–9) and with the compound scanner 4.3 (range 1–8). The diameter of the greatest follicle varied between 15 and 22 mm (mean 17.8). The second largest follicle was between 11 and 15 mm in diameter (mean 13.5, n = 11) and the third largest 6–15 mm (mean 10.5, n = 8). The correlation between the diameters of the greatest follicle as measured with the real-time and compound scanners was highly significant (r = 0.728, P < 0.001).

The oestradiol level in serum was strongly related to the diameter of the follicle as measured both with the real-time scanner (r = 0.661, P < 0.001) and with the compound scanner (r = 0.650, P < 0.001). When there were 4 or more follicles in the ovaries, the serum oestrogen level (4234 ± 737 pmol/l, mean ± SEM) was higher than when there were 1–3 follicles present (2874 ± 457 pmol/l, P = 0.05).

The ovarian size was measurable 1–5 days (mean 3.5) after initiation of the hMG treatment. The mean size of the ovaries at that time was 523 mm² (range 254–843). There was no significant difference in size between the right and left ovary. The ovarian size increased during the hMG treatment. At the time of the hCG injection, the ovaries had doubled in size (mean 1185 mm², range 393–2073). One week after induction of ovulation by hCG, the mean ovarian size 3425 mm² (range 1249–6476) was almost three times greater than that at the time of full follicular maturation. An ultrasound scan of an enlarged ovary one week after induction of ovulation is shown in Fig. 2. The ovarian size at that time was strongly correlated to the serum oestradiol level at the day of the hCG injection (r = 0.771, P < 0.001, Fig. 3). There was also a strong correlation between the serum oestradiol level and the ovarian size during hMG induction of follicular maturation (r = 0.652, P < 0.001).

The size of the uterus was measured in 5 patients and found to be 1691 mm² on average (range 1414–2203 mm²). Uterus increased in size during
the hMG treatment (mean 33 per cent, range 16–72) and in 4 of 5 patients also after induction of ovulation (mean 12 per cent, range 3–29).

One single pregnancy occurred during the gonadotrophin treatment. On the second day of hMG treatment a follicle with a diameter of 6 mm was visible (Fig. 4A). The next day it was 8 mm in diameter (Fig. 4B). At the time of hCG injection after 7 days of hMG treatment (75–150 IU/day) seven follicles were seen in the ovaries (Fig. 4C and D). The greatest follicle was oval with a mean diameter of 17 mm (14 × 20 mm). The diameters of the other follicles were 14 mm or less. A slight collapse of the dominant follicle was demonstrable 1 and 2 days after hCG injection (Fig. 4E and F). The ovaries were enlarged one week after hCG injection, being on average 2.7 times greater than at the time of hCG injection. At 26 days after hCG injection an amniotic sac was seen in the uterus, and the ovaries were still enlarged.

Discussion

This study shows that ultrasound can be used for direct observation of the daily growth of ovarian follicles during induction of follicular maturation by exogenous human gonadotrophins. The technique of ultrasound examination of growing ovarian follicles was described by Hackelöer et al. (1977) and Hackelöer & Robinson (1978), who also used it to study ovarian changes in a patient during treatment with human gonadotrophins. In the present study frequent ultrasound examinations of the pelvis were performed during human gonadotrophin therapy of 12 women with anovulatory infertility. The ovarian follicles could easily be visualized on the ultrasound scan in all but 3 women who were obese or had difficulties to fill the bladder sufficiently. In these 3 women it was some days impossible to define and measure the follicles. The comparison between the compound B-mode and real-time scanner showed that in some patients it was possible to find more follicles in the ovaries with compound B-mode scanning. However, in most patients the real-time scanner proved to give similar results and was equally effective as the compound scanner for measuring the follicular diameter and monitoring follicular growth during the stimulation by exogenous gonadotrophins.

Multiple follicles were found to develop in all but one of our 12 patients. This has been a frequent finding also in other ultrasonic studies of induced cycles. During clomiphene treatment, Thebault et al. (1980) found several follicles in 59 per cent of their patients and Queenan et al. (1980) demonstrated multiple follicles in both ovaries in all their subjects. During human gonadotrophin treatment, Nitschke-Dabelstein et al. (1980) described development of several follicles in 50 per cent of the cycles.

The daily growth rate of the follicles (2.8 mm, on average) was found to be similar to that described during the pre-ovulatory phase of the normal menstrual cycle (Renaud et al. 1980). It seems that the follicle has to reach a diameter of at least 15 mm before fertile ovulation can be induced by hCG. In an in vitro study of the microenvironment of the human follicle, McNatty et al. (1979) found that only follicles with a diameter of 18 to 25 mm had a granulosa cell complement consistent with ovulation. In the ultrasonic study of spontaneous and induced cycles by Smith et al. (1980) there were no conceptions if the Graafian follicle was less than 15 mm in diameter.
Longitudinal scans of the ovaries of patient M.J. (26 years old, 4 years of secondary amenorrhoea) examined with the compound scanner. A. Right ovary. One follicle, 6 mm in diameter, on the second day of hMG treatment. B. Right ovary. One follicle, 8 mm in diameter, on the third day of hCG treatment. C. Right ovary at the time of hCG injection. Four follicles after 7 days of treatment with hMG. The mean diameter of the greatest follicle was 17 mm (14 × 20 mm). D. Left ovary at the time of hCG injection. Three follicles. Mean diameter of the two greatest follicles 14 mm. E. Right ovary one day after hCG injection. A slight collapse is seen in the dominant follicle. F. Right ovary 2 days after hCG injection. A beginning enlargement of the ovary is visible.
Ovulation was induced in the present study when the serum oestrogen concentration was at a level consistent with follicular maturation. At that time the diameter of the dominant follicle ranged between 15 and 22 mm. In previous ultrasonic studies of normal or induced menstrual cycles, there has also been a great variation (11–30 mm) in the dimensions of the ovarian follicle on the day of presumptive ovulation (for references, see Introduction). The wide range in the diameter of the pre-ovulatory follicle makes it difficult to use ultrasound as the only method for monitoring human gonadotrophin therapy.

The exact time of ovulation is not always possible to predict and evaluate by ultrasound. A slight partial collapse of the dominant follicle may be seen 1–2 days after the hCG injection (Fig. 4E and F). Another ultrasonic sign of ovulation is opacification i.e. low amplitude echoes inside the follicle (O’Herlihy et al. 1980a). These echoes may be caused by blood clots during early organization and vascularization of the corpus luteum (Hackelöer et al. 1979). Sometimes, however, the follicle remains unchanged on the ultrasound scan. It is also possible to misdiagnose the corpus luteum as a follicle. Thus, ultrasound can not be used as the sole monitoring method when accurate identification of follicular maturation and ovulation is needed e.g. for collection of human oocytes for in vitro fertilization.

Serum oestrogen determinations were used to monitor the gonadotrophin treatment in the present study. The number of follicles, the diameter of the greatest follicle and the ovarian size on the ultrasound scans were all strongly related to the serum oestrogen level. Daily oestrogen determinations have proved to be very valuable for monitoring human gonadotrophin therapy (Brown et al. 1969; Gemzell 1976). The preliminary results with ultrasound examinations during gonadotrophin treatment suggest that it is not possible to replace daily oestrogen determinations by ultrasound for the routine monitoring of the treatment at present. The great variation in the size of the mature follicle makes it difficult to decide when to interrupt hMG treatment and induce ovulation by hCG. Daily oestrogen monitoring of gonadotrophin therapy prevents severe hyperstimulation but not multiple birth (Gemzell 1976). Ultrasound may be used as a complement to daily oestrogen determinations to prevent multiple pregnancies.

Clinical symptoms or signs of hyperstimulation did not occur in any of our patients. However, the ultrasonic examination revealed that during the induction of follicular maturation there was a marked enlargement of the ovaries. After induction of ovulation by hCG, there was a further dramatic increase in ovarian size. During the luteal phase of the induced cycle the ovaries were six times greater than during the first days of treatment. Uterus also increased in size during the induced cycle presumably as a reflection of the markedly raised oestrogen secretion. During the normal menstrual cycle there is also a variation in the size of the uterus, as shown by ultrasound by Piironen & Kahlola (1975).

Thus, modern ultrasound technology has made it possible to monitor follicular growth and maturation during spontaneous and induced menstrual cycles. The hormone levels in peripheral blood can now be directly correlated to morphological changes in the ovaries. The ultrasound technique will increase our knowledge of ovarian pathophysiology and hopefully improve our methods for treatment of anovulatory infertility. During human gonadotrophin therapy, ultrasound may be a valuable complement to daily oestrogen determinations particularly for prevention of multiple pregnancies.

Acknowledgments

A fellowship from Finland Academy is gratefully acknowledged by Pekka Ylöstalo. We wish to thank Ass. Professor Leif Wide, Margareta Hoffstedt and her assistants at the Hormone Laboratory, Department of Clinical Chemistry at the University Hospital for perfect service with daily oestrogen determinations and Mrs. Birgitta Bohman for expert secretarial assistance.

References


Received on December 2nd, 1980.