Role of Ultrasonography in Infertility Management : Ovulation Monitoring and Assisted Conception

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Infertility causes great stress to many couples. Most of those presenting with childlessness have reduced fertility, rather than absolute sterility, and many are likely to conceive spontaneously. In this "ultrasonographic monitoring of growing follicles, in ovaries to determine the day of ovulation and its coordination with time of intercourse" has a well established role in the management of 'unexplained infertility'. This study was conducted to find out its efficacy in our setup. 86 female's patients of unexplained infertility, with different post-marital time period, underwent ultrasonographic ovulation monitoring each with follow up for minimum of four menstrual cycles. Average follicular growth rate was 2 mm a day, which increased to 3 mm a day, two days prior to ovulation. Follicular diameter at the time of ovulation ranged from 22 mm to 27 mm with a mean of 24 mm. We observed ovulation in 79.2% of our patients. In 8.1% patient's dominant follicle ceased to grow beyond 18 mm size and gradually become atretic. Leutinized unruptured follicle was documented in 12.7% of our patients in whom follicular size reached to periovulatory range but did not rupture. Uterine endometrial thickness at the time of ovulation varied from 7 mm to 13 mm and multilayered appearance (triple line sign) was observed in 57.3% of patients. Overall conception rate was 16.3% whereas it was much more encouraging to see in 23.5% of patients who were in less than 5 years of their marriage. Keeping in view of easy to workup as out patient basis in large numbers of patient, less time consuming, promising results, cost effectiveness and non invasive nature of technique; ultrasonographic monitoring of ovulation is recommended as a part of management in all patients of unexplained infertility.

Keywords: Infertility, ultrasound, ovulation monitoring.

Introduction

Infertility is seldom, if ever, a physically debilitating disease. It may however, severely affect the couple's psychological harmony, sexual life and social function.[11]

Most childless couples must cope with difficult psychological, family and social problems. In one comprehensive study un-explained infertility was 26% overall, which was the highest cause of infertility among other factors and causes.[13]

The examination and treatment of infertility may pose additional psychological difficulties, interfere with sexual life of couple, and impose a financial burden on the family or on society.[9] In our setup childlessness cast a heavy shadow on physiological and social adequacy of the female and dimininsh its social standing.[9]

In this traumatic and emotional background the couples desperately seek different types of treatment etc. The Radiologist can help the treating gynecologist by abdominal ultrasonography which is cost effective, non-invasive and reliable. **Infertility**, its investigation and its treatment, has been referred to as '**an emotional rollercoaster'**. Optimism takes turns with despair. Ultrasonography plays an important role in various assisted reproductive techniques, used in the management of infertility. Patients of unexplained infertility with normal basic medical investigations can be helped with ovulation monitoring, by coordinating time of ovulation and intercourse for assisted conception.[12]

A series of tests are available to evaluate ovulation. Abdominal Ultrasonography can monitor the follicular growth in an ovary throughout the menstrual cycle and is a reliable method of assessing follicular maturation and ovulation. This study was carried out to assess the effectiveness of sonographic ovulation monitoring in management of our patients with 'unexplained infertility'.

Material and Methods

This prospective study was carried out in CMH Bahawalpur from Jan 2007 to Dec 2009. In this study 86 married female patients of 'unexplained infertility' were included in which 56 were wives of army personal and 30 were wives of civilian working in army.

Criteria for selection of patients were that all of these patients were of 'primary infertility' and they have no history of any gynecological problems like dyspareunia or difficulty in intercourse. Their husbands were having no penile, hormonal or sexual problem. None of patient had history of confirmed previous conception or loss of pregnancy. Preliminary investigations like pelvic ultrasonography, hysterosalpingography and hormonal profile (serum FSH, LH, and prolactin; serum progesterone; serum T_3, T_4 and TSH) were carried out in all of these patients and were reported to be 'within normal limits'. We divided these patients into three groups according to their age and post marital status i.e. number of years after marriage. Group 1: Age: 20-25 years with less than 5 years of marriage, Group 2: Age: 25 – 28 years with 5 – 10 years of marriage and Group 3: Age: 29 – 35 years and more than 10 years of marriage. The patients who used clomiphene citrate for ovulation

induction, within previous 06 months, were not included in this study. There was no bar for upper limit of number of attempts but the patients who did not follow the ovulation monitoring for minimum of four menstrual cycles were also excluded from the study.

Ultrasonographic monitoring of follicular development and ovulation was performed on these patients with 3.75 MHz convex probe, using per abdominal technique. On all of these patients, we started follicular growth monitoring on 8th or 9th day of menstrual cycle (counting day one from the beginning of menses) and followed it daily until ovulation took place or the follicle ceased to grow and become atretic. The follicle, whose size and rate of growth exceeded the others, was marked as '**dominant follicle**' and it was followed and measured on subsequent visits.

Follicular measurement involved taking three measurements, two in the sagittal plane and one in coronal plane, and then calculating mean follicular diameter by adding all these measurements and dividing it by three. [Mean follicular diameter (mm) = L + H + W / 3] Increase in mean follicular diameter of dominant follicle was recorded daily, till ovulation. The criteria we observed for sonographic confirmation of **ovulation** were as follows:

a. Disappearance of dominant follicle.
b. Collapse of dominant follicle with presence of internal echoes in it.
c. Presence of free fluid in cul – de – sac.

The couples were advised not to have intercourse before ovulation. After ovulation every patient was advised to have repeated intercourse for next 2 – 3 days. Confirmation of pregnancy was made in the patients who missed their subsequent menses both with 'urine for pregnancy test' and by demonstrating gestation sac in gravid uterus on ultrasonography.

Results

Out of 86 patients selected in this study, 34 were between 20 – 25 years (mean age 22) with less than 5 years of marriage, 29 were between 26 – 28 years (mean age 27) and in 5 – 10 years bracket and 23 were between 29 – 35 years mean age 31) having more than 10 years of marital life. (Table 1).

Table 1: *Grouping of patients according to age and post-marital status i.e. No. of years after marriage.*

Group and Age	No. of Years after Marriage	No. of Patients
GP 1 20 – 25 years	Less than 5 years	34
GP 2 26 – 28 years	5 – 10 years	29
GP 3 29 – 35 years	More than 10 years	23

In all of these patients, latest by 10th day of their menstrual cycle, there has been one follicle in any ovary, whose size and rate of growth was definitely more than other growing follicles, so that it could be marked as '**dominant follicle'**.

During early mid cycle average growth rate of the follicle was 2 mm a day and in about one third of our patients (35.3%) it increased to 3 mm a day, during last two days before the ovulation. At the time of ovulation follicular diameter was between 22 mm and 27 mm with a mean of 24 mm. (Table 2). **The average day of ovulation in those who conceived was 15 – 17 day and in those who did not conceive was 13 – 15 day.**

Table 2: *Follicular diameter at the time of ovulation.*

Follicular Diameter	No. of Patients	Percentage
22 mm	7	10.3%
23 mm	16	23.6%
24 mm	21	30.9%
25 mm	13	19.1%
26 mm	9	13.2%

In 7 patients (8.1%) dominant follicle ceased to grow beyond 18 mm size and gradually become atretic. In 11 patients (12.7%) growing follicle reached to periovulatory size but did not rupture. In all of these 18 patients findings were almost same on repeated follow-up studies. These patients were referred back to gynecologist for detailed hormone profile and whether they could be helped by 'medical ovulation induction'.

In all the 68 patients, who underwent ovulation, we found a linear, directly proportionate correlation between the size of the growing follicle and thickness of uterine endometrium. In our patient's uterine endometrial thickness varied from 7 mm to 13 mm at the time of ovulation. Multilayered appearance 'Triple line sign' due to growth of endometrial glands and their secretions was seen in 39 patients (57.3%).

Out of these 86 patients of primary infertility, selected for sonographic evaluation monitoring, 14 patients (16.3%)

Table 3: *Group wise distribution of the patients who conceived.*

| Group	Total No. of Patients	No. of Patients Conceived	Percentage
GP 1	34	8	23.5%
GP 2	29	5	17.2%
GP 3	23	1	4.3%
Total	86	14	16.3%

conceived. Their group wise distribution is shown in Table 3.

Discussion

Infertility is defined as 1 year of unprotected inter-course without conception. Although it is reasonable to wait 1 year to begin the infertility evaluation for young couples with no history suggestive of reproductive disorder, it is reasonable to begin workup sooner in couples with history of lowering fertility or advancing age.[11]

Hackeloer and coworker more than 20 years back demonstrated the direct correlation between follicular growth observed by ultrasonography and circulating estradiol – 17B concentrations in spontaneous ovulatory cycles. It has been documented by many authors that the dominant follicle is the major source (greater than 90%) of circulating estradiol-17 B in spontaneous cycles.

Un – explained infertility is an ill-defined entity where no obvious cause of infertility could be determined. To some extend it depends on extent and complexity of investigation available.[13] McClure and Tompson in their study found that un-explained infertility was one of the important treatable cause of infertility i.e. 26% as shown in the chart. Fig. 1.
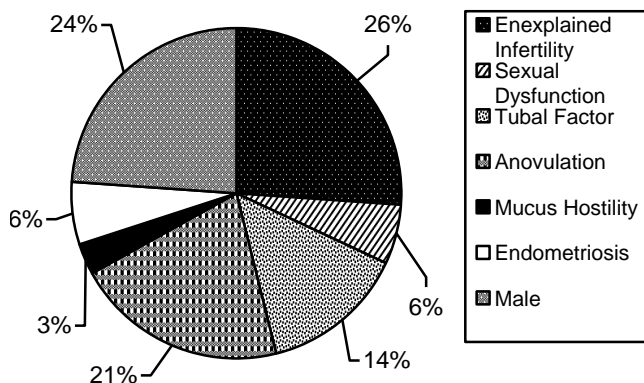
Fig. 1:

In our setup gynecologist and radiologist can work as a team to help infertile couples. The abdominal ultrasound is a non-invasive procedure which does not need any particular preparation and females won't be shy to undergo this simple out patient examination. In patients of unexplained infertility with normal clinical examination, pelvic ultrasonography, hysterosalpingography and hormone levels in blood; ovulation monitoring is helpful to coordinate the time of ovulation and intercourse. It enhances the chances of pregnancy and is called 'assisted conception'.

Four clinical methods commonly used to determine the ovulation are:

1. **Basal body temperature record.**
2. **Hormone assay.**
3. **Endometrial biopsy.**
4. **Ultrasonographic monitoring.**

Progesterone is thermogenic. An adequately recorded **basal body temperature record,** can suggest the day of ovulation but intercurrent illnesses, which alter the body temperature, make interpretation of such a chart difficult.[1]

Development of **radioimmunoassay** has allowed precise documentation of estrogen, FSH and LH throughout the menstrual cycle. A change in the pattern of plasma concentration of these hormones, can determine the day of ovulation[2] but this is not cost effective.

Serial **uterine endometrial biopsies**, by showing the cyclical hormone related changes in endometrium can point out the day of ovulation with ± 2 days accuracy[1]. This is an invasive and relatively non-specific technique.

Hackeloer and colleagues first described **ultrasonographic monitoring of growing follicle and ovulation** in 1979.[3] By the days 5 to 7 of a menstrual cycle small developing follicles measuring 5 to 6 mm in diameter become visible in ovaries. They appear as rounded echo free structures with well defined smooth margin. In subsequent days, size and rate of growth of one follicle exceeds the others and it is labeled as '**dominant follicle**' (Fig. 3). Other follicles become atretic usually below the 14mm size. Growth of dominant follicle is monitored till the time of ovulation.

Just before ovulation, with lutenizing hormone (LH) surge, the outer cellular layer of follicle becomes edematous and is separated from granulosa layer to produce a fluid track through which extrusion of oocyte cumulus complex occurs (Fig. 4). Immediately after ovulation the follicle is collapsed and filled with echogenic blood to become corpus luteum (Fig. 4). Collapse of dominant follicle with development of small amount of fluid in cul-de-sac, confirms the **ovulation**.
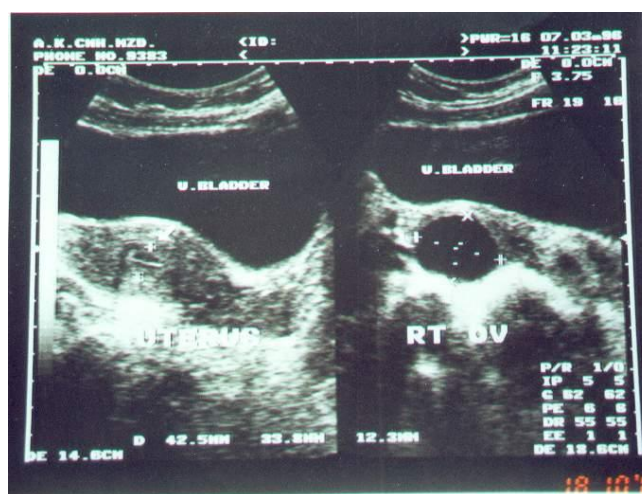
Fig. 2: *A growing follicle in right ovary and multilayered appearance of thick uterine endometrium in peri-ovulatory days of menstrual cycle.*

Fig. 3: *Fluid track in right ovary due to lutenizing hormone surge just prior to ovulation.*

Fig. 4: *Corpus luteum formation in right ovary after ovulation.*

In periovulatory period **uterine endometrium** is thickened and has multilayered ('triple line') appearance due to growth and secretions of endometrial glands.

Range of follicular diameter at the time of ovulation, mentioned in literature, is 18 – 28 mm.[4] In our study lowest diameter at which ovulation took place was 22 mm and maximum follicular size we observed at the time of ovulation was 27 mm. Average remained 24mm, which is comparable to international studies.[4]

Review of literature revealed **follicular growth rate** of 1 – 2 mm / day.[4] We observed the same in our study except that during last 2 days prior to ovulation, in about one third of our patients, follicular growth rate increased to 3 mm / day. This periovulatory increase in growth rate is not mentioned in available literature.

In 8.1% patients, in our study, **dominant follicle ceased to grow** beyond 18 mm size and gradually become atretic. Polan and his colleagues observed similar phenomenon in 11% of patients in a study carried out in 1982 and found it to be due to asynchrony between estrogen peak and LH surge.[5]

We observed **lutenized unruptured follicle** in 12.7% of our patients, in whom follicle size reached into periovulatory range but did not rupture. Daly and his colleagues have reported it in 29% of patients in a similar ultrasound study.[6] Ovum entrapment in unruptured follicle has been reported in 6% to 79% of cycles as assessed at laproscopy; in differrent studies.[7]

Cyclic uterine endometrial changes, we noted during proliferative phase and at the time of ovulation in our patients were comparable to those mentioned in literature.[4]

In our study, 14 patients out of 86 conceived (16.3%). **Conception rate** was better of patients Group – 1 who were 18 – 25 years of age with less than 5 years of their marriage (23.5%). Conception rate in a similar study carried out in Birmingham Women's Hospital, Birmingham, UK by Dr. Khaldoum Sharif was 40%.[8] Better conception rate in their study can be attributed to their better medical facilities and more educated and cooperative patients.

Conclusions

Infertility affects approximately 10 – 15% of couples and is a medical concern for women of reproductive age. Ovulation monitoring by ultra-sonography in un-explained infertility has promising results in assisted conception techniques to overcome infertility. Out of the tests used to evaluate the ovulation, except ultrasound monitoring which is real time and shows actual event of development of follicle to ovulation other tests like basal body temperature record, measurement of serum hormone levels and uterine endometrial biopsy – all are indirect, expansive and time consuming tests.

Ultrasonographic monitoring of ovulation is important as it shows the actual event of development of simple follicle into dominant follicle and ovulation that is extrusion of oocyte cumulus from the follicle. It has additional advantage of documenting uterine endometrial thickness changes in response to ovarian hormones. This non-invasive technique, in our set up can benefit lot of couples of urban and rural population who are reluctant or unable to afford to visit these expensive **Specialized Fertility Clinic** and undergo invasive techniques including TVG and Color Doppler which are costly equipments and need trained staff etc. Secondly majority of these couples are unaware when to have intercourse to have the highest changes of conception. In our study we realized how essential the sex education is to get better results. Taking into account above mentioned benefits, cost effectiveness and non invasive nature of technique, ultrasonographic monitoring of ovulation is recommended as a part of management in all patients of unexplained infertility.

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