Polycystic ovarian syndrome: a follow-up study on fertility and menstrual pattern in 149 patients 15–25 years after ovarian wedge resection

Ottar Lunde1,4, Ole Djøseland2 and Per Grøttum3

1Department of Gynaecology and Obstetrics, 2Laboratory of Endocrinology, Medical Department, The National Hospital and 3Department of Informatics, University of Oslo, Oslo, Norway

4To whom correspondence should be addressed at: Department of Gynaecology and Obstetrics, The National Hospital, 0027 Oslo, Norway. E-mail: ottar.lunde@rikshospitalet.no

BACKGROUND: The aim of this study was to evaluate fertility and menstrual pattern in women with polycystic ovarian syndrome (PCOS) 15–25 years after ovarian wedge resection (OWR). METHODS AND RESULTS: The diagnosis was based on the combination of ovarian pathology and symptoms. The 149 patients, all primarily treated at a university teaching hospital, were studied three times by means of a questionnaire up to 25 years after surgery. Kaplan–Meier analysis showed a cumulative rate of spontaneous pregnancies of 76%, increasing to 88% when induced pregnancies were included. The cumulated live birth rate was 78%. A bootstrap simulation indicated that 69.5% would develop post-operative adhesions, which could impede pregnancy in 13.4%. In the majority of the patients a regular menstrual pattern was restored up to 25 years after OWR. CONCLUSION: The results of OWR in PCOS are favourable to most modern treatments. Laparoscopic electrocautery of the ovaries is the only method equally successful, and, by being less invasive, it has made OWR history in the treatment of PCOS.

Key words: adhesions/menstrual pattern/ovarian wedge resection/polycystic ovarian syndrome/pregnancy rate

Introduction

Prior to 1980, laparotomy with OWR was the only treatment of polycystic ovarian syndrome (PCOS) (Stein and Leventhal, 1935).

The introduction of clomiphene citrate in the 1960s created a new and effective method by which the operation could be avoided and pregnancy achieved (Macgregor et al., 1968). In patients not responding to the operation, the intervention per se seems to enhance the clomiphene effect (Goldzieher, 1981; Campo, 1998).

Reports of post-operative adhesions, which constitute an additional factor of infertility, resulted in a more cautious attitude towards OWR (Kistner, 1969; Buttram and Vaquero, 1975; Toaff et al., 1976).

Campo et al. demonstrated in 1983 a successful laparoscopic approach for clomiphene-resistant PCOS patients by wedge resection of ovarian tissue performed through multiple biopsies (Campo et al., 1983). By the use of electrocautery the ovulatory effect and pregnancy rate was even better (Gjønnaess, 1984).

In the 1980s purified FSH, laparoscopic electrocauterization or laser drilling of the ovaries with or without clomiphene, follicle-stimulating hormone (FSH) alone or combined with IVF, have been the treatment of choice (Naether and Fischer, 1993; Gjønnaess, 1994; Naether et al., 1994; Donesky and Adashi, 1995).

Materials and methods

Patients

During the period from 1970 to 1980, 149 patients fulfilled the diagnostic criteria for inclusion in this study: multicystic ovaries at gross examination and two or more of the symptoms of menstrual irregularity, hirsutism, infertility or obesity (Lunde, 1981; 1982; 1984; Lunde and Grøttum, 1984; Lunde et al., 1988, 1989).

In 1980, 1984 and 1995 the patients were asked to answer a detailed questionnaire about their clinical status. They concomitantly signed an informed consent according to the Helsinki Committee requirements. In several cases the information was controlled when patients presented themselves at our outpatient clinic.

Fertility

The patients were asked about the number of pregnancies, year of delivery, outcome of the pregnancy and use of any ovulatory drugs. The date of the last period was mandatory for the first pregnancy...
after OWR. Written statements concerning their health and their pregnancies were collected from the various hospitals and doctors which they had previously visited, including reports on later abdominal intervention, i.e. laparoscopic second-look, tubal surgery or sterilization as well as Caesarean section.

At OWR the condition of the internal genital organs, uterus and adnexae were evaluated and described as follows: apart from polycystic ovaries, 0 = normal, 1 = scattered adhesions without any possible interference with fertility, 2 = more widespread adhesions with obscure significance, 3 = massive adhesions, probably incompatible with fertility. Descriptions from later surgery were evaluated using the same criteria. The adhesion score was calculated as the mean of the adhesions in both adnexae.

In order to study the risk of inducing additional infertility factors by OWR, patients without adhesions at OWR and no subsequent known pelvic inflammatory disease were investigated at primary Caesarean section and at tubal sterilization.

**Menstrual pattern**

At OWR menstrual cycles were classified as follows: 1 = regular (flow at intervals <35 days), 2 = oligomenorrhoea (35 days < intervals <90 days), 3 = oligoamenorrhoea (3 months < intervals <6 months), 4 = secondary amenorrhoea (more than 6 months since the last period), 5 = primary amenorrhoea (above 18 years of age and no spontaneous vaginal bleeding) (Lunde, 1982). In the questionnaire the patients were requested to elaborate on the regularity of their periods, the average interval from the beginning of one to the start of the next, and the shortest and the longest. In addition, the duration of the bleeding and the amount of the flow were recorded.

**Statistical analysis**

The BMDP statistical package (BMDP Statistical Software Inc., Los Angeles, CA, USA) was employed for the statistical analysis. Mean and range are used for descriptive statistics. Pair- and groupwise comparisons were performed using the t-test with separate variances. Fisher’s exact test was used for analysing 2×2 tables. The confidence interval for one proportion was calculated using standard normal approximation. Kaplan–Meier analysis was used to estimate time-accumulative rates.

Bootstrapping was used to assess the variation in the incidence of adhesions after OWR and the resulting effect on pregnancy. In bootstrapping the original data are resampled to create a large number of replicate datasets from which measures of variability like SEM and confidence intervals can be estimated (Davison and Hinkley, 1997). The resampling simulates the randomness when a group of patients is assembled from the population. By repeating the resampling one simulates the assembly of several study groups, which form a basis for the statistical estimation of variability. Bootstrapping is an alternative to complex parametric analysis, which in some cases can be error-prone. In the experiments, cells with 0 observations were allocated a value of 0.5 before bootstrapping. After 100 000 repetitions confidence intervals were calculated from the bootstrap distribution using the 2.5 and the 97.5 percentiles. The frequencies of some cells could not be determined experimentally and were therefore estimated from assumed similarities with observed cells. For each bootstrap the simulated probabilities of the observed cells were applied to corresponding unobserved cells as has been previously described (Aalen et al., 1997). To test the sensitivity to this assumed similarity the probabilities of the unobserved cells were perturbed by a random error. This was accomplished by the following procedure: (i) generate a new set of cell counts in the observed cells by resampling the data with the original cell probabilities, (ii) from these counts calculate the logit-function for the pair of observed cells which act as template

for an unknown pair of cells, (iii) add a random error drawn from a normal distribution with mean 0 and SD of 0.5 to the logit function and calculate the resulting probabilities in the unknown cells, (iv) generate the cell counts in the unknown cells by sampling with the thus obtained cell probabilities, (v) repeat the procedure for all unknown cells, (vi) repeat steps i–v, 100 000 times and calculate the 95% confidence interval (CI) from the simulated data. The median cell probability remains unchanged using this procedure. The SD of the error of 0.5 was chosen so that the cell probabilities varied within a reasonably large range.

**Results**

Information was obtained for all 149 patients in 1980. The corresponding numbers for 1984 and 1995 were 142 patients (95%) and 136 (91%) respectively.

Twenty patients had no wish for children, infertile partner, genital alteration beyond surgical repair or hysterectomy within a year after OWR. The remaining 129 patients had desire and assumed capability of attaining pregnancy. As shown in Table I, 78 of these patients became pregnant spontaneously one or several times. Pregnancies occurred both spontaneously and upon induction with gonadotrophins, clomiphene citrate or bromergocryptine in 12 patients. However, this additional treatment was an arbitrary response to heavy patient demand only a few months after OWR or delivery. Therefore these patients are considered as spontaneously ovulatory. An additional three patients became spontaneously pregnant after secondary tubal surgery. Fifteen patients achieved pregnancy only after administration of ovulatory drugs. Spontaneous pregnancy thus occurred in 72% (93/129). When taking non-respondents into account along with cases of natural or operative menopause, a Kaplan–Meier analysis showed a cumulative proportion of spontaneous pregnancies of 76% (95% CI 68.7–84.7%). Induced pregnancies were not recorded in this analysis. These included, the cumulative pregnancy rate was 88.0% (95% CI 81.7–94.2%).

Among the 254 pregnancies registered, 218 occurred after spontaneous ovulation (86%) resulting in 156 of the 190 children (82%). One pair of twins was observed among these, and 36 induced, one twin and one triplet emerged, giving a frequency of multiple pregnancies of 0.5 and 6.0% respectively.

Due to various reasons (marital, social, use of ovulatory drugs), the interval from OWR to pregnancy could only be evaluated in 60 spontaneously ovulating patients. The mean interval was 22.5 months. A total of 50% became pregnant within 1 year. After 4 years 88% had conceived.

The mean interval between deliveries in 39 patients who gave birth to two children and conceived spontaneously was 35.9 months. This was significantly less (P = 0.006) than the 54 months reported in a reference material of 22 normal women (Lunde et al., 1989).

In 218 non-induced pregnancies 34 ended as spontaneous abortions. Ten of them occurred in the second trimester and were thus unlikely to be caused by PCOS. This gives a frequency of spontaneous abortions of 11% (24/218). In induced pregnancies the rate was 14% (5/36).

Ectopic pregnancies occurred nine times in six patients, corresponding to an incidence of 3.5% (9/254). However, two
took place after normal deliveries, ascribing OWR as a possible releasing factor in only four of the six patients, which by Kaplan–Meier analysis gives an OWR related incidence of 5.1% (95% CI 1.1–9.0%) in the 129 patients.

Among 108 pregnant patients, 11 spontaneously ovulating and one induced did not deliver a living child, corresponding to an overall live birth rate of 74% (96/129). Using a Kaplan–Meier analysis as previously described the cumulative live birth rate was 78.2% (95% CI 70.5–85.9%).

Adhesions were seen and dealt with at OWR in 14 (11%) of the 129 patients. The mean adhesion score was 1.46 (0.5–3.0). Twelve of these achieved pregnancy later on. There was no significant difference in the cumulative pregnancy rate between the patients with adhesions at OWR and those without. In the 115 patients without, the subsequent development of adhesions could be evaluated only indirectly. Before any assessment of post-OWR alterations could be made, four patients developed intra-abdominal diseases that were likely to cause adhesions (cancer and peritonitis) and were therefore excluded from the analysis. Data from the remaining 111 patients are shown in bold numbers in Figure 1a. Infertility persisted in 21 patients (18.9%) after OWR, and 11 chose a second-look operation where adhesions were seen in all of them with a mean score of 2.05 (1–2.5). After removal of adhesions, three of these delivered children. Adhesions were evaluated in 38 of the remaining 90 patients, mainly at Caesarean section and sterilization. In 24 of these adhesions had developed with a mean score of 1.48 (0.5–2.5), which was significantly lower than in the 11 patients with persisting infertility after OWR ($P = 0.01$).

To estimate the overall adhesion rate among the 111 patients and the effect on pregnancy, a bootstrap procedure was used. It was initially assumed (i) that adhesions were similar in the infertile patients who sought surgery (p-s+ branch) and those who did not (p-s-) and that the pregnancy rate would have been the same given surgery and (ii) that the adhesion rate was similar in the fertile patients subjected to secondary surgery (p+s+) and those who were not (p+s-). The resulting estimates after performing 100 000 bootstraps on the original data are shown in Figure 1a. For the outermost branches mean values and 95% CI are given, in regular typeface for the observed cells and in italics for the unknown cells. In Figure 1b these data are regrouped to indicate more clearly to what extent adhesions (a+) would develop in a group of patients undergoing OWR, how this would affect the chance of getting pregnant (p+, p-) and to what extent secondary tubal surgery (second-look) could improve the outcome for those not obtaining pregnancy initially. The upper numbers indicate the frequencies and 95% CI. A total of 69.5% (95% CI 56.2–82.1%) would develop adhesions following OWR (a+). In those patients 18.5% (95% CI 11.4–26.1%) would not achieve pregnancy initially (a-p+). After surgical removal of adhesions (second-look), infertility would persist in 13.4% (95% CI 6.4–20.9%). In patients without adhesions after OWR only 0.8% (95% CI 0.0–3.9%) would not achieve pregnancy (a-p-).

To assess how sensitive the results were to the underlying assumptions of the same relative frequencies in corresponding sections of the tree, the bootstrapping was repeated but with a random departure from the hypothetical similarity as described in the methods section. The resulting effect on the unobserved cell probabilities is indicated in Figure 1b by the lower numbers which represent the 95% CI. In the group with post-operative adhesions who remained permanently infertile (a+p-p) the 95% CI did not change perceptibly (from 6.4–20.9% to 6.1–21.1%).

Table II shows the menstrual pattern of the 149 patients at OWR and delineates the factors influencing the evaluation in 1995. Thirteen (8.7%) had their uterus removed, usually because of fibroids and intractable bleeding irregularities. However, in five instances the reason was pre- and malignant genital disease. Natural menopause had occurred in 23 patients, nine patients were taking hormonal substitution and in 13 patients data were missing. Based on a conservative estimate where the missing patients were included in the denominator a beneficial effect of OWR was found in 82% (81/99, 95% CI 74–89%).

**Discussion**

The pregnancy rate after classical OWR in PCOS shows great variations. A mean pregnancy rate of 58.8% has been reported...
Figure 1. The development of post-ovarian wedge resection (OWR) adhesions and their effect on pregnancy in patients without peroperative adhesions. (a) Observed data and an example of simulated data. p+/−: pregnant and not pregnant. s+/−: having and not having secondary surgery with assessment of adhesions. a+/−: adhesions present and not present. Observed numbers of patients are in bold. In 52 patients who initially became pregnant (p+) and 10 patients who did not become pregnant (p−), no post-operative assessment of adhesions was performed (s−). The rate of adhesions could only be indirectly estimated in these patients. This was done by bootstrapping and based on two assumptions: (i) that adhesions were similar in the infertile patients who sought surgery (p+s− branch) and those who did not (p−s−) and that the pregnancy rate would have been the same given surgery and (ii) that the adhesion rate was similar in the fertile patients subjected to secondary surgery (p+s+) and those who were not (p+s−). The results of the simulation are shown as mean and 95% confidence interval, in italics for the groups where no data were available and in regular typeface for the observed groups. (b) Regrouped data. The data from the simulation are reassembled to indicate how adhesions (a+, a−) would develop in a group of patients undergoing OWR, how this would affect the chance of getting pregnant (p+, p−) and to what extent secondary tubal surgery (second look) could improve the outcome for those not obtaining pregnancy initially. The upper numbers indicate the frequencies and their 95% confidence intervals under the assumption of similarity described above. The lower numbers are the 95% confidence intervals obtained when adding a random uncertainty to the assumption of similarity (see Materials and methods for details).

(Donesky and Adashi, 1995) whereas Stein holds the record of 86.7% (Stein, 1966). The cumulative rate in the current study was 76.7%, increasing to 88%, when including patients who post-OWR only conceived due to ovulatory drugs.

The fear of OWR causing additional infertility factors was heavily debated throughout the 1970s (Kistner, 1969; Buttram and Vaquero, 1975; Toaff et al., 1976). Evaluation of adhesions with respect to fertility is difficult. Meticulous inspection by an experienced gynaecologist is mandatory; nevertheless the prediction of future pregnancy is conflicting. Obviously OWR could cause adhesions, which might interfere with fertility. However, the extent of such interference remains uncertain.

In an attempt to assess the possibility of complications caused by the procedure a bootstrap simulation was performed on the current data. The results indicate that adhesions after OWR occur in as much as 2/3 of the patients and prevent pregnancy in 1/4 of these. However, if adhesions are removed, permanent infertility persists only in 13–14% of the total number of patients. Although the average adhesion score was higher in these patients than in the 14 with adhesions at OWR, there was a considerable overlap in the adhesion score and together with the very low fecundity rate (3/11 versus 12/14) this might
Population at large. In a meta-study Campo (1998) reported this delineated in Table II. Apart from primary amenorrhoea, also seen in conceptions achieved by means of ovulatory drugs, the intervals between the first and the second deliveries in this study were significantly less than in a reference material (Lunde, 1981). Although there is no information on the use of contraception or deliberate family planning in any of these studies, the intervals per se ought to be regarded as a meaningful indicator of the menstrual cyclicity in 1995, 15–25 years after OWR, the mean period before conception being in concert with that published (Adashi et al., 1981).

The live birth rate in operative treatment of PCOS has not been published previously. In drug and IVF therapy a fairly realistic rate is 30% per treatment and on a cumulative basis >50% within 1–3 cycles (Bergh et al., 1995). The rate of 72% in the current study, conservatively estimated, could have been higher. Based on new knowledge and experience of the past, in cases complicated with primary amenorrhoea, obesity and insulin-resistance other primary therapy might have been preferable. Interestingly, the current findings confirm the cumulative conception rate of 73% after 10 years as previously predicted (Adashi et al., 1981).

Both significance and duration of post-OWR menstrual regularity and ovulatory activity have been analysed previously (Stein, 1964; Rhodes, 1968; Kirstner, 1969; Lunde, 1981). One source claims that improvements were temporary, whereas others show continuity.

The menstrual cyclicity in 1995, 15–25 years after OWR, is delineated in Table II. Apart from primary amenorrhoea where the results were poor, the beneficial effect seems independent of the menstrual situation at the time of surgery. With regular periods, regular ovulations are not a certainty but it represents a strong evidence of frequent ovulatory activity. The post-OWR ovulatory frequency was not studied. However, the intervals between the first and the second deliveries in this study were significantly less than in a reference material (Lunde et al., 1989). Although there is no information on the use of contraception or deliberate family planning in any of these studies, the intervals per se ought to be regarded as a meaningful indicator of the menstrual cyclicity in 1995, 15–25 years after OWR, the mean period before conception being in concert with that published (Adashi et al., 1981).
significant proof of normal and lasting ovulatory activity after OWR.

The relationship between PCOS and menopause cannot be fully assessed in the present study as only 15% of the patients had reached menopause at the end of the study period. The average age of these patients was 45 years, whereas the average age of the still menstruating patients was 46 years.

It has been stated that laparoscopic induced ovulation, use of clomiphene and gonadotrophins alone or in combination with IVF, the leading therapies of the last two decades, have not added any improvement where pregnancy rate is concerned (IVF can be reserved for less appropriate cases or if surgery fails. It has been stated that laparoscopic induced ovulation, use of clomiphene and gonadotrophins alone or in combination with IVF, the leading therapies of the last two decades, have not added any improvement where pregnancy rate is concerned (Donesky and Adashi, 1995).

The surgical intervention on polycystic ovaries has during the years varied from unilateral extirpation, uni- or bilateral wedge resection, and multiple biopsies to electrocautery and laser-punctures. It is tempting to speculate that several aetiologic factors may cause an increased ovarian volume and that a correction of this, irrespective of the underlying cause, will abate the consequences of the disease. In the current study the wedge removed was of such a size that the ovaries were reduced to an apparently normal volume (Lunde, 1982). The importance of the volume is reflected in its correlation to the duration of symptoms, body mass index and ovarian morphology in untreated patients (Lunde et al., 1988). A significant correlation between the effects on menstruation and ovulation and the number of uni-polar cautery spots employed on the ovaries has been reported (Gjønnes, 1984). Histological evaluation after unipolar cauteterization of the ovaries has documented severe tissue loss (Van der Weiden, 1987). These findings confirm the significance of the ovarian mass and its reduction. The beneficial effect of volume reduction on ovulation and pregnancy rate has been documented by ultrasound measurement of ovarian volume before and after drilling (Tulandi et al., 1996).

Despite the good results, OWR’s invasive nature cannot be neglected. After the laparoscopic route of ovarian surgery was demonstrated, OWR was made medical history in the treatment of PCOS. It has been shown that laparoscopic treatment can give excellent results regarding infertility as well as menstrual disturbances, and recently that the improvements are lasting (Gjønnes, 1994, 1998). Surgical treatment has the great advantage of being an occasional procedure with few complications and lasting effect on infertility and menstrual disturbances, thus giving relief from the nuisance of unpredictable periods. Therefore the patients may plan their pregnancies to come without medical aid. Although drugs alone or combined with IVF can solve the problems of PCOS, the therapy has the disadvantage of symptom recurrence by cessation. That surgery can cause adhesions and in a few cases tubal incompetence is undisputed. However, the latter can nowadays be overcome by IVF and should be a minor problem as compared with the benefit for the majority of patients who can be spared for years from close medical supervision. Unopposed oestrogen stimulation/chronic anovulation, the basic problem in PCOS, has been associated with endometrial cancer, diabetes mellitus and cardiovascular diseases (Coulam et al., 1983; Dahlgren et al., 1992; Gibson, 1995; Pettigrew and Hamilton-Fairley, 1997; Solomon, 1999). A lasting reduction of the oestrogen stimulation by OWR might possibly reduce the likelihood of associated diseases in the future (Coulam et al., 1983; Pierpoint et al., 1998). It has been stated (Donesky and Adashi, 1995) that surgical treatment should be the last resort in PCOS after failure of medical therapy. Neither the current study nor others (Gjønnes, 1994, 1998; Li et al., 1998) support this cautious attitude. One might reconsider the obvious advantageous results of operative intervention, taking into account the inexpensiveness of the procedure (Li et al., 1998). Drugs and IVF can be reserved for less appropriate cases or if surgery fails.

Acknowledgements
We would like to thank Professor Odd O.Aalen for helpful statistical advice and Professor Knut Bjørn for his pertinent criticism of the manuscript.

References


Received on November 7, 2000; accepted on March 23, 2001