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WOMEN'S HEALTH

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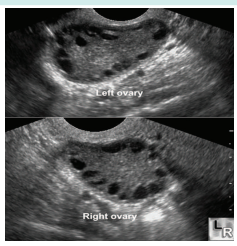

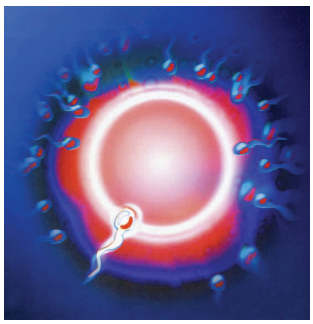

Editorial Note:

Dear Doctor,

It's our immense pleasure to inform you that we have published our newsletter, "Women's Health". In this issue we are focusing on modern approach to postmenopausal hormonal replacement therapy and polycystic ovarian syndrome management.

Hope these are enriched your knowledge. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.

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WOMEN'S HEALTH

A modern approach to postmenopausal HRT: trading bleeding with safety

The menopause is a natural event and marks the end of reproductive function. The diagnosis of estrogen deficiency symptoms is easy and so is the required treatment. HRT is just what it means - the replacement of missing hormones. Women's trust in the use of HRT was shattered in July 2002 when the world media disclosed the 'consequences' of treating menopausal women with HRT. The lay media dealt with the findings and sought specialists' opinion even before the medical journal concerned published the data. The resulting confusion drove the majority of women to discontinue a much-suited treatment that maintained their quality of life. The data were criticized due to the less than careful analysis with questionable principles adopted for recruitment into the trial. A fixed combination of estrogen and a progestagen was given to women between the age of 50 and 79 years old, a fifth of whom were 70–79 years. The recruited population was a mixture of past users of HRT, as well as treatment-naive women. Furthermore, some women enrolled into the trial were asymptomatic, as well as those who suffered symptoms of estrogen deficiency. The expectations of the steering committee were simplistically optimistic in that a single preparation would be used by all women and 'one size fits all' would be at hand to cure all ills.

Evolution of HRT regimens

Estrogen deficiency symptoms were successfully treated with unopposed estrogen in women with intact uteri until 1975, when publications suggested that, in addition to irregular bleeding, such treatment increased the risks of endometrial hyperplasia and carcinoma. In the UK, adding synthetic progestagen (or a progestin) for 7 days each month was already practiced, albeit not universally, to reduce the incidence of irregular bleeding. (For the rest of this editorial, progestagen(s) will refer to both progestin(s) and progestagen(s). Formal publications followed to confirm this approach. Further studies attempted to optimize the dose and duration of the progestagen, during each 28–30-day cycle of continuous estrogen would regulate the withdrawal bleeding and reduce the incidence of endometrial hyperplasia and carcinoma. However, unscheduled bleeding on sequential combined HRT and the development of premenstrual tension-like symptoms (e.g., dysphoria, bloatedness and fluid retention) remained a clinical challenge.

"An appropriately adjusted estrogen regimen cures almost all menopausal symptoms, protects against osteoporosis and, when used in women younger than 60 years, may half the risk of cardiovascular disease … and cognitive impairment…"

The experienced clinician would try to adjust the dose and duration of the progestagen, using the mini-pill, for example, to optimize the regimen for the individual woman and, as such, enhance long-term concordance with HRT. The provide a predefined combination package for which a license was granted.

The call on progestagens to resolve the bleeding problem

The re-establishment of a monthly bleed was met with resentment from many women who felt 'liberated' from the monthly chore when they reached the menopause. In addition, the health economists viewed the introduction of HRT in postmenopausal women, with its possible unscheduled bleeding leading to further assessment and gynecological referral, as pressure on resources. Given the perceived benignity of progestagens at those times, their utility in continuous dosing with estrogen was promoted as 'it could only do good to women' and a new concept was born. The industry proceeded in earnest to develop continuous combined HRTs (ccHRTs) as non-bleeding regimens. The introduction of 'bleed-free HRT' had fulfilled this particular demand of women and made doctors feel better able to manage women without the potential referral for the management of unscheduled bleeding.

"A mounting body of evidence points the finger at continuously added progestagens as the antagonizing factor to the beneficial effects of estrogen."

Sequential combined HRT was relegated to junior women in the menopause transition and ccHRT became the reward of seniority. The other buzz phrase used to promote ccHRT was the reduction of endometrial hyperplasia and cancer. The sense of satisfaction with this achievement prevailed despite the fact that unscheduled bleeding in women using ccHRT affected more than half of the users during the first 3 months and 20% of women continued to experience irregular bleeding after 6 months of use.

Many women discontinued treatment due to progestagen-associated adverse effects, particularly dysphoria and perpetual sense of premenstrual tension. Several developments followed where the progestagen was administered parentally, including transdermal patches and vaginal rings releasing progestagens, as well as vaginal progesterone cream, but all failed to eliminate the adverse effects of the endometrial protector. Even the levonorgestrel (LNG)-loaded intrauterine contraceptive device is associated with high systemic absorption and corresponding adverse effects. The mean serum LNG level in LNG-loaded intrauterine contraceptive device users is equivalent to the serum levels achieved by two LNG mini-pills daily.

At the height of HRT popularity, only a third of hysterectomized women (estrogen-only users) or those with intact uteri used the treatment for more than 12 months. This cannot be explained by fear of adverse effects alone, and suitability of a given hormone product and/or its dose deserves serious consideration.

Progestagen use is at fault

The clinical trials and the observational studies published during the last decade pointed to the 'causal' relationship of ccHRT with increased risks of breast cancer, stroke, heart attacks and dementia. The menopause is a natural event and marks the end of reproductive function. The diagnosis of estrogen deficiency symptoms is easy and

These estimates were systematically challenged by prominent statisticians worldwide. The presumed increased risk of strokes, heart attacks and dementia were not found as exaggerated by the initial reports and were mainly related to old age at initiation of treatment.

The increased risk of breast cancer and that of dementia with ccHRT remained unresolved. The data that have emerged from estrogen-only therapies have clearly indicated that estrogen is not only breast cancer risk neutral, but there were also reduced risks in hysterectomized women. This reduction continued after 10.7 years of follow-up. When comparing the incidence of breast cancer in the placebo arms of WHI trials, it is of note that these women were themselves at a higher risk of developing breast cancer compared with those with intact uteri. Unlike the data with ccHRT, the incidence of dementia in the WHI estrogen-only study was not statistically significantly different from those on placebo. A mounting body of evidence points the finger at continuously added progestagens as the antagonizing factor to the beneficial effects of estrogen.

Ligand activation of progesterone receptor

Traditional teaching in medicine, particularly in the hormone contraceptives literature, emphasizes the mitogenic and thrombogenic effects of estrogens, although the thrombogenic effect was not found in association with transdermally administered estradiol. Indeed, even the US FDA classified estrogen as a carcinogen. On the other hand, progestagens are depicted as 'harmless' therapeutics with their metabolic and cellular effects being largely trivialized.

Cellular synthesis of progesterone receptors (PRs) is a function of a fully activated estrogen receptor. Ligand activation of PR-A and -B accelerates their nuclear depletion through ubiquitination and proteasomal degradation, reduces estrogen receptor synthesis and activates 17β-hydroxysteroid dehydrogenase. The latter accelerates the catabolism and inactivation of intracellular estrogen. Hence, the ligand-activated PR exerts the antagonistic effect on endometrial glandular proliferation, but at the same time it induces endometrial stromal proliferation. By contrast, breast glandular proliferation is stimulated under the influence of progesterone and progestagens. Therefore, a continuous antagonistic effect of estrogen action in other tissues may not be as beneficial as seen in the endometrium and may well be harmful.

Progestagens bind other nuclear receptors

Administered progesterone or progestagens activates PR-A and -B to various degrees in a cell and tissue context. As steroidal compounds, their administration results in varying degrees of androgen, glucocorticoid and mineralocorticoid receptors' activation; hence, the recognized adverse effects of the progestagens.

"Longevity has increased so rapidly during the last century and the menopause is considered a mid-life, rather than end-of-life event. Indeed, women are expected to work for longer and the pension age will soon be raised to 70 years."

Clinically, a progressively unfolding story is the long-term effect of continuously administered progesterone and its analogs, through glucocorticoid receptor activation, on neurons. Continuous treatment with glucocorticoids reduces neural plasticity and spine formation in hippocampal and nucleus accumbens connections.

Other effects of continuous exposure to progestagens include a variable degree of adverse effects on glucose and lipids metabolism, as well as vascular reactivity. Furthermore, depot progestagens and high progestagen-containing contraceptive pills reduce vaginal immunity and enhance oncogenic transformation of human papilloma virus. One explanation being the interaction of these synthetic compounds with the glucocorticoid receptor response element in the open reading frame of human papilloma virus types 16 and 18 that encode E6 and E7 oncoprotein formation."

Quality of life & the menopause

Menopausal symptoms of hot flushes, night sweating, insomnia, panic attacks, depressive moods, emotional lability and loss of libido are inconvenient enough to undermine quality of life. Genitourinary symptoms may develop early in the menopause transition, thus adding to the woman's distress. Longevity has increased so rapidly during the last century and the menopause is considered a mid-life, rather than end-of-life event. Indeed, women are expected to work for longer and the pension age will soon be raised to 70 years. An appropriately adjusted estrogen regimen cures almost all menopausal symptoms, protects against osteoporosis and, when used in women younger than 60 years, may half the risk of cardiovascular disease and cognitive impairment.

In women with intact uteri, endometrial protection is required. The woman needs to understand these complicated risk issues through friendly websites and informed consultations, thus enabling her to make informed health choices. Women concerned about the deterioration of their quality of life, if appropriately informed, will accept the re-establishment of withdrawal bleeding as a reasonable trade off for long-term safety of a much-needed HRT. The clinician needs to learn how to confidently manage unscheduled bleeding and learn how to help women make a safe choice in the management of the menopause. In optimizing individualized sequential combined HRT, one aims for an adequate estrogen dose that cures menopausal symptoms in combination with the cyclical sequential progesterone, or progestagens, using the lowest effective dose for a short duration each month that ensures regular bleeding. In adopting this principle with the currently available preparations, the woman is cured of her symptoms, the bleeding pattern becomes more tolerated and the risks of long-term treatment are minimized.

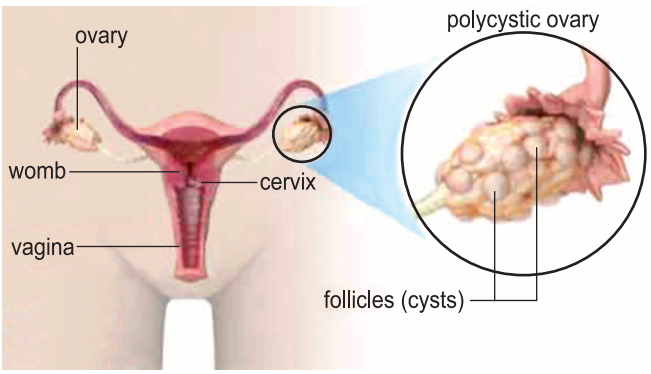
References: Smith D, Prentice R, Thompson D, Herman W. Association of exogenous estrogen and endometrial carcinoma. N. Engl. J. Med. 293, 1164–1167 (1975).

WOMEN'S HEALTH

Evidence-based management of infertility in women with polycystic ovary syndrome using surgery or assisted reproductive technology

Surgical treatment in the form of ovarian wedge resection by laparotomy was first proposed for the treatment of infertility in women with polycystic ovary syndrome (PCOS) by Stein and Leventhal in 193. However, this procedure was later largely abandoned, despite promising outcomes of initial series, owing to the risk of post operative adhesions and substantial loss of ovarian tissue, and was supplanted by the use of medical ovulation induction agents such as clomifene citrate and gonadotropins. However, surgical approaches to ovulation induction have continued to play a part in the management of infertility associated with PCOS both in the form of laparoscopic ovarian diathermy, essentially a less traumatic modern version of ovarian wedge resection, and bariatric surgery. Surgical approaches to infertility are largely restricted to cases of anovulation, usually associated with PCOS, and include laparoscopic ovarian drilling/diathermy (LOD) and bariatric surgery for morbid obesity and infertility. Assisted reproduction is normally used as a third-line treatment for those suffering from infertility associated with anovulation and is also more widely used for couples with other causes of infertility including male infertility, tubal damage or unexplained infertility.

When assessing response to treatment for infertility it is important to differentiate between the various outcome measures. This review will provide information concerning live-birth rate, pregnancy rate and ovulation rate when this information is available. The preferred outcome method is the live-birth rate per cycle started when considering IVF treatment, but this is not available in many of the publications in this area. Results are frequently reported as ongoing pregnancy rate or other outcomes that are less relevant to clinicians and patients who are trying to select their optimum treatment.



LOD

LOD, a less invasive modification of ovarian wedge resection, was first described in women with PCOS by Gjønæss in 1984 who reported ovulation and pregnancy rates as 92 and 58%, respectively. Since this time, LOD using both electrocautery (diathermy) and laser vaporization has been performed to create multiple (four to ten) puncture holes in the ovarian cortex and stroma; the mechanism of action is poorly understood but is believed to be similar to that of ovarian wedge resection with destruction of ovarian androgen-producing thecal cells, leading to local (conversion of androgenic intrafollicular environment to an estrogenic one) and systemic (reduction in serum levels of androgens and lutenizing hormone together with an increase in follicle-stimulating hormone levels) endocrine changes that are thought to promote follicular recruitment, maturation and subsequent ovulation. In a narrative review reporting on the efficacy of LOD based predominately on observational studies, the spontaneous ovulation and pregnancy rates ranged from 54 to 76% and 28 to 56% at 6 months, and 33 to 88% and 54 to 70% at 12 months, respectively (Box 1).

The most current systematic review and meta-analysis of randomized controlled trials (RCTs) examining all RCTs of infertile clomiphene citrate-resistant (CCR) women with PCOS undergoing LOD did not identify any RCTs comparing LOD with placebo/no treatment. However, there were five RCTs (338 CCR randomized patients) comparing LOD (6–12 months of follow-up) versus gonadotropin ovulation induction (three to six treatment cycles), and meta-analysis showed no difference in live-birth rate per patient, ongoing pregnancy rate per patient, ovulation rate per patient, miscarriage rate per pregnancy or quality of life between the two interventions, but there was a reduction in multiple pregnancy rate per ongoing pregnancy (1 vs 17%, respectively; odds ratio [OR]: 0.13; 95% CI: 0.03–0.59) with LOD in CCR PCOS patients. There were also less direct costs with LOD compared with gonadotropins.

Therefore, LOD has been recommended by an expert international consensus group as second-line therapy in CCR PCOS. A subsequent RCT, also supporting this recommendation, has demonstrated no difference between LOD and up to six cycles of clomifene citrate in terms of live birth, pregnancy, ovulation and miscarriage rates in therapy-naive women with PCOS. Two RCTs with conflicting results have compared metformin to LOD in CCR PCOS. The first of the RCTs to be published compared metformin to LOD in 120 overweight (BMI 25–30 kg/m^2) CCR women with PCOS with follow-up over 6 months and found no difference in ovulation rate per cycle (55 vs 53%; $p > 0.05$) or clinical pregnancy rate per patient (72 vs 56%; relative risk [RR]: 1.28 with 95% CI: 0.99–1.70 favoring metformin) but a reduced miscarriage rate per pregnancy (15.4 vs 29%; $p < 0.05$), higher live-birth rate per patient (59 vs 36%; RR: 1.63 with 95% CI: 1.08–2.46) and lower costs (50 vs €1050; $p < 0.05$) with metformin.

The later RCT to be published compared metformin with LOD in 110 CCR PCOS patients with a mean BMI of 36 kg/m^2 who were also insulin resistant, with follow-up over 6 months or 30 weeks (whichever occurred first). In this study, metformin was less efficacious than LOD with a reduced ovulation rate per cycle (33 vs 51%; RR: 2.05 with 95% CI: 1.4–2.9; $p = 0.001$), pregnancy rate per cycle (4 vs 8%; RR: 2.19 with 95% CI: 1.03–4.63; $p = 0.03$), and cumulative pregnancy rate per patient (20 vs 38%; RR: 2.47 with 95% CI: 1.05–5.81; $p = 0.03$) in conjunction with a higher proportion of patients who never ovulated (33 vs 14%; RR: 2.85 with 95% CI: 1.11–7.29; $p = 0.02$) but no difference in first trimester miscarriage rate per pregnancy (18 vs 19%; RR: 1.05 with 95% CI: 0.16–6.9; $p = 0.09$).

Box 1. Laparoscopic ovarian drilling.

Background

- Surgical ovarian wedge resection by open laparotomy was one of the first treatments for anovulation due to PCOS

First report

- LOD procedure was first described by Gjønæss in 1984 Techniques
- Four to six punctures per ovary using either electrocautery (diathermy) or laser vaporization

Mechanism of action

- Poorly understood but believed to be via destruction of ovarian androgen-producing thecal cells leading to local and systemic reduction in androgen levels thus promoting follicular growth and ovulation Indications
- Anovulatory PCOS women with CCR, particularly when there are other indications for laparoscopy

Results at 6 months

- Spontaneous ovulation rate: 54–76%
- Pregnancy rate: 28–56%

Results at 12 months

- Spontaneous ovulation rate: 33–88%
- Pregnancy rate: 54–70%

Predictors of poor success

- Morbid obesity (BMI >35)
- Marked biochemical hyperandrogenism (serum T ≥4.5 nmol/l)
- Duration of infertility >3 years
- LH/FSH ratio <2.0 (i.e., low basal LH levels)

Advantages

- No requirement for monitoring as no increased risk of multiple pregnancy

Disadvantages

- Possible short-term effect
- Surgical risks of laparoscopy, general anesthesia and ovarian damage including (rarely) ovarian atrophy, failure and adhesion formation

CCR: Clomiphene citrate resistance; FSH: Follicle-stimulating hormone; LH: Lutenizing hormone;
LOD: Laparoscopic ovarian drilling/diathermy; PCOS: Polycystic ovary syndrome.
Data taken from [1–3].

The same group of researchers who published the first of the RCTs comparing metformin with LOD subsequently conducted a RCT comparing metformin combined with clomifene citrate with LOD, and reported a higher ovulation rate per cycle (72 vs 56%, respectively; p = 0.023) and lower cost of treatment (119.6 vs US$316.8, respectively; p < 0.001) but no difference in cumulative pregnancy rate (61 vs 62%, respectively; p = 1.0), miscarriage rate per pregnancy (17 vs 13%, respectively; p = 1.0) or cumulative live-birth rate (52 vs 54%, respectively; p = 1.0) in 55 randomized CCR PCOS patients with a mean BMI of 30 kg/m^2 (all had a BMI <35 kg/m^2) over 6 months follow-up. Despite a risk of postoperative adhesions following LOD, a single RCT has shown that a second-look laparoscopic adhesiolysis performed 3 months following LOD in CCR women with PCOS has no benefit in terms of pregnancy or miscarriage rates per patient over 6 months follow-up.

In summary, LOD is recommended as a second-line therapy in CCR PCOS patients and is an alternative to gonadotropin therapy with equal efficacy but lower risk of multiple pregnancy and cost. There is conflicting evidence as to whether metformin alone or LOD is more beneficial in terms of reproductive outcome. Based on a single small RCT with a primary end point of live-birth rate and sample size defined arbitrarily, there was no evidence of a difference in pregnancy or live-birth rate between 6-months treatment with either clomifene citrate combined with metformin or LOD.

Bariatric surgery

Bariatric or weight-loss surgery in the general population results in approximately 15–30% weight loss that is sustained in the long term. A Cochrane review of bariatric surgery in the general population found that such surgery resulted in greater weight loss than conventional treatment in obesity (BMI >30 kg/m^2) and a reduction in comorbidities such as diabetes and hypertension based on three RCTs and three prospective cohort studies. However, this review did not assess fertility outcomes. Another systematic review of bariatric surgery in the general population assessed reproductive outcomes and reported that case-control and cohort studies show improved fertility and a reduction in obstetrical complications such as gestational diabetes, macrosomia and hypertensive disorders of pregnancy, but the incidence of intra-uterine growth restriction appears to be increased. No conclusions could be drawn regarding the risk of preterm labor and miscarriage.

Assisted reproductive technologies in the patient with PCOS

Stimulated intrauterine insemination

The first published report on intrauterine insemination (IUI) was in 1962. IUI has since become a widely used fertility treatment, with the rationale for its use being to increase the conception rate in infertile couples by increasing the chance that the maximum number of healthy sperm reaches the site of fertilization in the fallopian tube.

Based on a lack of RCTs comparing the pregnancy rates of IUI versus timed intercourse during ovulation induction in women with PCOS, a consensus by a group of international experts concluded that combining IUI with ovulation induction may be considered in anovulatory women with PCOS where there is associated male factor infertility or failure to conceive despite successful induction of ovulation. The efficacy of such treatment ranges from 11 to 20% clinical pregnancy rate per cycle with a multiple pregnancy rate ranging from 11 to 36% based on a limited number of studies on women with PCOS.

Since this consensus report, a RCT comparing three consecutive cycles of clomifene citrate ovulation induction with either IUI or timed intercourse as first-line treatment for anovulatory infertility in 188 therapy-naive women with PCOS (525 cycles) with a BMI <30 kg/m^2, patent fallopian tubes and a male partner with normal semen analysis has been published.

This study showed comparable outcomes between the two treatment groups with no difference in clinical pregnancy rate per cycle (8.5 vs 7.9%; p = 0.26) or per woman (23.6 vs 22.1%; p = 0.33), miscarriage rate per pregnancy (18.1 vs 19.0%; p = 0.31) and livebirth rate per woman (19.3 vs 17.9%; p = 0.33), respectively. Therefore, the addition of IUI to the first three cycles of clomifene citrate ovulation induction does not improve reproductive outcomes for the PCOS woman where anovulation is the sole cause for infertility.

WOMEN'S HEALTH

IVF

The first successful human birth from IVF treatment was that of Louise Brown who was born in the UK on 25 July 1978 [21]. Since this time, IVF treatment has been developed to include injections of gonadotropins to achieve multifollicular ovarian development for subsequent egg retrieval, fertilization of eggs and the generation of embryos for transfer into the uterus. The success rates of IVF treatment has improved over time and, in 2005, 34% of cycles resulted in a clinical pregnancy and 28% of cycles a live birth, although success rates depend on the patient's age, with the highest pregnancy rates observed in women under 35 years of age where pregnancy and live-birth rates approach 43 and 37%, respectively. Risks involved with IVF treatment include multiple pregnancy, when multiple embryos are transferred, and a significant risk of ovarian hyperstimulation syndrome (OHSS).

However, the risk of multiple pregnancy is more easily controlled with IVF than ovulation induction with gonadotropins, because with IVF the number of embryos transferred into the patient's uterus can be restricted to one or two, with cryopreservation of other good quality embryos for future use, whereas with ovulation induction it is not possible to completely avoid ovulation of more than one oocyte from smaller follicles.

Anovulation alone, in principle, is not an indication for IVF/intracytoplasmic sperm injection (ICSI) and therefore IVF/ICSI treatment in women with PCOS is recommended either as a third-line treatment (after failed first- or second-line therapies including clomifene citrate, gonadotropin or LOD ovulation induction) or in the presence of other infertility factors such as tubal damage, severe endometriosis or male factor infertility.

IVF/ICSI treatment in women with PCOS poses a number of clinical challenges, in particular that of moderate-to-severe OHSS, with a risk of approximately 10% compared with a risk of 0.5–4.0% observed in the general IVF population. A meta-analysis has reported an OR of 6.8 (95% CI: 4.9–9.6) for the development of OHSS in ultrasound-determined PCOS patients compared with those with normal-appearing ovaries on baseline ultrasound.

Women with PCOS achieve pregnancy and live-birth rates similar to those of non-PCOS patients during conventional IVF cycles, as evidenced by a large systematic review and metaanalysis of nine observational studies comparing 458 women with PCOS (793 cycles) with 694 matched controls (1116 cycles). However, women with PCOS have a higher cycle cancellation rate prior to egg collection (13 vs 4%; OR: 0.5 with 95% CI: 0.2–1.0) due to absent/limited ovarian response or increased risk of OHSS. Women with PCOS also have a higher number of eggs collected (random effects weighted mean difference: +3.4 eggs with 95% CI: 1.7–5.1) and a lower fertilization rate resulting in no difference in the number of fertilized eggs compared with non-PCOS patients. The miscarriage rate per pregnancy was similar between PCOS and non-PCOS patients. In most of the studies, the incidence of OHSS was not clearly reported and therefore data regarding this risk were difficult to pool.

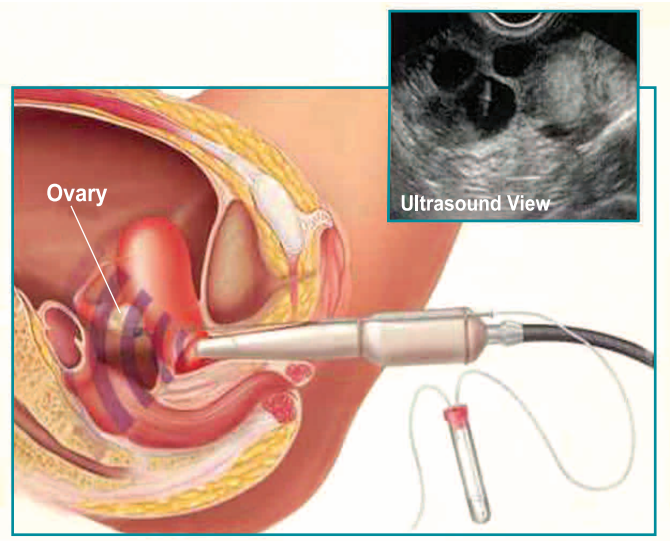


Table 1. UK uptake of IVF and success rates (2006–2008).

	2006	2007	2008	Change 2007–2008 (%)
Number of cycles	44,275	46,829	50,687	+8.2
Number of patients	34,855	36,861	39,879	+8.2
Number of babies born through IVF	10,242 successful births giving rise to 12,596 babies	11,091 successful births giving rise to 13,672 babies	12,211 successful births giving rise to 15,082 babies	Births up +10.1, babies +10.3
IVF live-birth rate per cycle started	23.1%	23.7%	24.1%	+0.4
Multiple birth rate following IVF	22.7%	23.0%	23.2%	+0.2

Data taken from [101].

In 2011, a systematic review and meta-analysis of eight RCTs compared the gonadotropin-releasing hormone antagonist protocol with the long gonadotropin-releasing hormone agonist protocol in 783 randomized women with PCOS undergoing IVF/ICSI treatment. This review found no difference in ongoing pregnancy rates (OR: 0.91; 95% CI: 0.67–1.22) or clinical pregnancy rates (OR: 0.87; 95% CI: 0.64–1.19) per woman, respectively, but there was a 10% lower risk of OHSS per woman with the antagonist protocol (risk difference: -0.10; 95% CI: -0.14 to -0.07). Therefore in the IVF/ICSI treatment of women with PCOS, the antagonist protocol would seem to be preferred to the long agonist protocol owing to the lower risk of OHSS, with no difference in reproductive outcomes. Overall success rates for IVF can be derived from the large UK Human Fertilization and Embryology Authority database. The success rates of IVF treatment have improved over time. The database showed a livebirth rate for IVF of 24.1% per cycle starting in 2008, an increase of 0.4% over the 2007 data.

Data for 2006–2008 are shown in TaBle 1. A recent publication from the USA has identified final assisted reproductive technology success rates using cumulative pregnancy and live-birth rates, showing that cumulative live-birth rates in excess of 50% can be achieved for patients under 40 years of age after cumulative transfer of six embryos.

Future perspective

The best evidence to date on reproductive outcomes in women with PCOS supports LOD as second-line medical therapy in CCR women, and IVF/ICSI as third-line medical treatment or in the presence of other infertility factors.

Further RCTs are required to assess the effectiveness and safety of LOD and other secondline medical treatments such as metformin, with or without clomifene citrate, and gonadotropins in CCR women with PCOS. RCTs are also required to determine the efficacy and safety of bariatric surgery in the anovulatory PCOS woman with obesity.

There is a lack of high-quality evidence concerning bariatric surgery for anovulation. In our opinion, there is a window of opportunity to recruit such patients into adequately powered, high-quality RCTs on this topic, and all patients undergoing bariatric surgery for treatment of anovulation should be entered into an international registry to allow accumulation of further information on this developing topic.

References: 1. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am. J. Obstet. Gynaecol. 29, 181–191 (1935). Unlu C, Atabekoglu CS. Surgical treatment

Congratulations !

The Winners of WOMEN'S HEALTH *Quiz Competition* Vol-5 No-4 July-Sept 2012

Dr. Hosna Zari Tahmina (Akhi)
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