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Funding: This work was supported by a grant from the Royal Brompton and Harefield NHS Trust Clinical Research Committee (No 2000CS022B).

Conflict of interest: None declared.

Ethical approval: Not required.

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(Accepted 6 November 2003)

doi 10.1136/bmj.37938.645220.EE

Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial

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BMJ 2004;328:192-5

Abstract

Objective To compare the effectiveness of an electrocautery strategy with ovulation induction using recombinant follicle stimulating hormone in patients with clomiphene resistant polycystic ovary syndrome.

Design Randomised controlled trial.

Setting Secondary and tertiary hospitals in the Netherlands.

Participants 168 patients with clomiphene citrate resistant polycystic ovary syndrome: 83 were allocated electrocautery and 85 were allocated recombinant follicle stimulating hormone.

Intervention Laparoscopic electrocautery of the ovaries followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted, or induction of ovulation with recombinant follicle stimulating hormone.

Main outcome measure Ongoing pregnancy within 12 months.

Results The cumulative rate of ongoing pregnancy after recombinant follicle stimulating hormone was 67%. With only electrocautery it was 34%, which increased to 49% after clomiphene citrate was given.

Subsequent recombinant follicle stimulating hormone increased the rate to 67% at 12 months (rate ratio 1.01, 95% confidence interval 0.81 to 1.24). No complications occurred from electrocautery with or without clomiphene citrate. Patients allocated to electrocautery had a significantly lower risk of multiple pregnancy (0.11, 0.01 to 0.86).

Conclusion The ongoing pregnancy rate from ovulation induction with laparoscopic electrocautery followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted, or recombinant follicle stimulating hormone, seems equivalent to ovulation induction with recombinant follicle stimulating hormone, but the former procedure carries a lower risk of multiple pregnancy.

Introduction

Polycystic ovary syndrome is characterised by oligomenorrhoea or amenorrhoea, infertility, hirsutism,



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Table 1 Personal characteristics of women allocated electrocautery strategy or ovulation induction with recombinant follicle stimulating hormone. Values are numbers (percentages) of women unless stated otherwise

Characteristics	Electrocautery (n=83)	Recombinant follicle stimulating hormone (n=85)
Mean (SD) age (years)	28.5 (3.7)	28.7 (4.1)
Type of infertility:		
Primary	63 (76)	64 (75)
Secondary	20 (24)	21 (25)
Parity:		
Nulliparous	64 (77)	66 (78)
Multiparous	19 (23)	19 (22)
Mean (SD) duration of infertility (years)	2.8 (2.2)	2.8 (2.1)
Mean (SD) body mass index	27.9 (6.3)	27.3 (8.8)
Mean (SD) waist to hip ratio	0.83 (0.09)	0.84 (0.08)
Mean (SD) luteinising hormone to follicle stimulating hormone ratio	1.99 (0.96)	1.93 (0.90)
Mean (SD) testosterone (nmol/l)	4.0 (1.7)	3.9 (1.3)
Mean (SD) free androgen index	14.0 (10.5)	13.3 (10.2)
Mean (SD) volume of ovaries (ml)	10.6 (4.5)	11.6 (6.5)
Mean (SD) total motile sperm count ($\times 10^6$)	108 (136)	96 (106)

acne, and bilaterally enlarged, cystic ovaries.^{1 2} The syndrome affects 4-9% of women of childbearing age.³ Infertility due to chronic anovulation is the most common reason for women seeking counselling or treatment. The drug of first choice for inducing ovulation is clomiphene citrate, taken orally, although 20% of women fail to ovulate.⁴

Ovulation induction with gonadotrophins is well established in patients resistant to clomiphene citrate, but extensive monitoring is necessary because of the high sensitivity of polycystic ovaries to exogenous gonadotrophins, with the risk of multiple follicle development leading to termination of the cycle, ovarian hyperstimulation syndrome, or multiple pregnancy.⁵ To reduce these complications, various dose regimens have been used.⁶ A chronic low dose step up regimen is probably the most efficient and safest treatment at present.⁷

Recently, laparoscopic electrocautery of the ovaries has been introduced as an alternative treatment. This involves a single procedure, with minimal morbidity, which can lead to consecutive ovulations, which has minimal risks of multiple pregnancy.⁸ Patients may also respond to clomiphene citrate after this treatment.^{9 10} Disadvantages are the need for surgery under general anaesthesia, the unknown long term effects on ovarian function, and possible adhesion formation.

Patients who fail to ovulate after electrocautery of the ovaries and clomiphene citrate can still be treated with gonadotrophins, before proceeding to the costly and burdensome procedure of in vitro fertilisation and embryo transfer. Whether gonadotrophins or electrocautery should be the treatment of choice in patients with clomiphene citrate resistant polycystic ovary syndrome is still debatable. The three comparative studies that have been published in this area have methodological flaws that weaken the conclusions.¹¹⁻¹³

We conducted a randomised controlled trial to compare the effectiveness of an electrocautery strategy with ovulation induction against recombinant follicle stimulating hormone in women who had clomiphene citrate resistant polycystic ovary syndrome.

Methods

Our trial took place between February 1998 and October 2001 in 29 Dutch hospitals. Women were invited to participate if they had chronic anovulation and polycystic ovaries, diagnosed by transvaginal ultrasonography.¹⁴⁻¹⁶ They had also to be resistant to clomiphene citrate—that is, show persistent anovulation after taking 150 mg clomiphene citrate daily for five days. Primary exclusion criteria were other causes of infertility, including severe male factor subfertility and age over 40 years.

Women were randomly allocated to either laparoscopic electrocautery of the ovaries followed by clomiphene citrate and recombinant follicle stimulating hormone if anovulation persisted, or ovulation induction with recombinant follicle stimulating hormone. The two treatments are described in detail on bmj.com.

The primary end point was ongoing pregnancy within 12 months, defined as a viable pregnancy of at least 12 weeks. Secondary end points were ovulation, miscarriage, ectopic pregnancy, multiple pregnancy, and live birth.

We designed our study as a non-inferiority trial for pregnancy rates because of the anticipated benefits of electrocautery. Assuming an ongoing pregnancy rate within 12 months of 38% after treatment with gonadotrophins, with an α of 5% and a β of 20%, and expecting a pregnancy rate of 52% with the electrocautery strategy, we required 168 patients to exclude a difference of 5% or more to the detriment of electrocautery of the ovaries.^{17 18}

Results

Overall, 168 patients were finally eligible for inclusion in our study, of which 83 were allocated to the electrocautery strategy and 85 to recombinant follicle stimulating hormone. Forty five patients allocated to electrocautery had persistent anovulation or recurrence of anovulatory cycles during follow up and received clomiphene citrate; 21 of these subsequently received recombinant follicle stimulating hormone, and two started recombinant follicle stimulating hormone directly after electrocautery. No differences

Table 2 Pregnancy outcomes at 12 months in 83 women allocated to electrocautery strategy and 85 allocated to ovulation induction with recombinant follicle stimulating hormone. Values are numbers (percentages) of women unless stated otherwise

Treatment regimen	No of women	Pregnant	No of miscarriages*	No of multiple pregnancies	Ongoing pregnancy	No of premature deliveries	Live births
Electrocautery strategy:							
Electrocautery	83 (100)	31 (37)	3	—	28 (34)	—	28 (34)
Electrocautery and clomiphene citrate	45 (54)	14 (31)	1	—	13 (29)	—	13 (29)
Electrocautery, clomiphene citrate, and recombinant follicle stimulating hormone	23 (28)	18 (78)	3†	1	15 (65)	3	12 (52)
Electrocautery strategy: total	83	63 (76)	7	1	56 (67)	3	53 (64)
Recombinant follicle stimulating hormone	85	64 (75)	7	9	57 (67)	6	51 (60)

* <12 weeks.

† Includes one ectopic pregnancy.

were observed between the treatment groups at baseline (table 1).

The ongoing pregnancy rate in both groups at 12 months was 67% (rate ratio 1.01, 95% confidence interval 0.81 to 1.24). We found no significant difference in pregnancy rates between the two treatment arms over 12 months (log rank score 0.25, $P=0.62$; figure). Table 2 summarises the outcomes of pregnancy.

Of the 56 (67%) ongoing pregnancies in the electrocautery group, one resulted in quintuplets in a patient also given recombinant follicle stimulating hormone; successful embryo reduction led to the live birth of twins. Neither electrocautery alone nor subsequent treatment with clomiphene citrate resulted in multiple pregnancy.

Of the 57 ongoing pregnancies in the women allocated recombinant follicle stimulating hormone, eight were twin pregnancies and one was a triplet pregnancy. Neonatal death occurred in one of the twin pregnancies at 26 weeks' gestation. The triplet pregnancy ended with premature delivery at 22 weeks.

No patient had perioperative complications or ovarian hyperstimulation syndrome. Ovulation induction with recombinant follicle stimulating hormone, resulted in significantly more multiple pregnancies than with the electrocautery strategy (rate ratio 0.11, 0.01 to 0.88).

Discussion

An electrocautery strategy was as effective as recombinant follicle stimulating hormone alone for inducing ovulation in patients with clomiphene citrate resistant polycystic ovary syndrome. Although the ongoing pregnancy rate after six months was lower after electrocautery alone than with recombinant follicle stimulating hormone, this difference was abolished after administration of clomiphene citrate and recombinant follicle stimulating hormone when anovulation persisted, leading to cumulative ongoing pregnancy rates of 67% in both groups. We cannot, however, exclude small differences, as our power calculation was based on lower expected pregnancy rates after recombinant follicle stimulating hormone and after the electrocautery strategy than were observed in both arms of the study. We believe that our power calculation was informative and justifiable, but the

What is already known on this topic

Polycystic ovary syndrome is the most common ovulatory disorder

Patients with polycystic ovary syndrome resistant to clomiphene citrate are treated with recombinant follicle stimulating hormone or laparoscopic electrocautery of the ovaries

What this study adds

An electrocautery strategy and ovulation induction with recombinant follicle stimulating hormone are both effective at inducing ovulation

Multiple pregnancies can largely be avoided by electrocautery and clomiphene citrate before recombinant follicle stimulating hormone

confidence intervals are wide and do not exclude the 5% difference.

Our results provide a scientific basis for counselling patients with clomiphene citrate resistant polycystic ovary syndrome, particularly as many fail to respond to treatment. We have shown that both the electrocautery strategy and recombinant follicle stimulating hormone are effective at inducing ovulation, with comparable cumulative pregnancy rates at 12 months. No cases of ovarian hyperstimulation syndrome were occurred, and miscarriage rates were comparable between treatment arms.

The major difference between the two strategies is that multiple pregnancies can largely be prevented by treating women with electrocautery and clomiphene citrate before recombinant follicle stimulating hormone. Although there is a need to minimise the frequency of multiple pregnancies, so far there has been little effort to issue guidelines or regulations.¹⁹ Our study may be a first step towards reducing multiple pregnancies while maintaining good pregnancy rates.

We thank M M Denyn and V I Mauer for their invaluable assistance. Also see bmj.com for colleagues who included and treated the patients.

Contributors: See bmj.com

Funding: Serono Benelux provided financial support for recombinant follicle stimulating hormone during the first eight

months of the study when this drug was not funded by the health services. FvdV was supported by a grant from the Health Insurance Funds Council (OG 97/007), Amstelveen, Netherlands.

Competing interests: None declared.

Ethical approval: The study was approved by the institutional review boards of all participating hospitals.

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(Accepted 6 November 2003)

Outbreak of severe acute respiratory syndrome in a tertiary hospital in Singapore, linked to an index patient with atypical presentation: epidemiological study

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Abstract

Objective To describe an outbreak of severe acute respiratory syndrome (SARS) in a tertiary hospital in Singapore, linked to an index patient with atypical presentation, and the lessons learnt from it.

Design Descriptive study.

Setting A tertiary hospital in Singapore.

Participants Patients, healthcare workers, and visitors who contracted SARS in Singapore General Hospital.

Main outcome measures Probable SARS as defined by the World Health Organization.

Results The index patient presented with gastrointestinal bleeding, initially without changes to his chest radiograph. Altogether 24 healthcare workers, 15 patients, and 12 family members and visitors were infected. The incubation period ranged from three to eight days. Only 13 patients were isolated on their dates of onset.

Conclusions Atypical presentation of SARS infection must be taken into consideration when managing patients with a history of contact with SARS patients. The main gap in the containment strategy in this outbreak was the failure to identify the index patient as someone who had been discharged from a ward in another hospital that managed probable SARS cases. Strict infection control measures, a good surveillance system, early introduction of isolation procedures, and

vigilant healthcare professionals are essential for controlling outbreaks.

Introduction

On 6 March 2003 the Ministry of Health in Singapore issued a press release that three Singaporeans had developed atypical pneumonia after travelling to Hong Kong.¹ Around the same time, the World Health Organization issued a global health alert on severe acute respiratory syndrome (SARS), an atypical pneumonia that has been associated aetiologically with a novel coronavirus, SARS-COV.² We describe an outbreak in a tertiary hospital delivering acute care in Singapore that was linked to an index patient with atypical presentation and highlight the lessons learnt in managing the outbreak.

Methods

We used data from the period of 24 March to 15 April 2003. We describe the epidemiological link of 51 patients infected directly or indirectly by an index patient in Singapore General Hospital, a tertiary hospital delivering acute care.

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BMJ 2004;328:195-8



This is the abridged version of an article that was posted on bmj.com on 15 January 2004 <http://bmj.com/cgi/doi/10.1136/bmj.37939.465729.44>