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Does suppressing luteinising hormone secretion reduce the miscarriage rate? Results of a randomised controlled trial

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Abstract

Objective—To determine whether prepregnancy pituitary suppression of luteinising hormone secretion with a luteinising hormone releasing hormone analogue improves the outcome of pregnancy in ovulatory women with a history of recurrent miscarriage, polycystic ovaries, and hypersecretion of luteinising hormone.

Design—Randomised controlled trial.

Setting—Specialist recurrent miscarriage clinic.

Subjects—106 women with a history of three or more consecutive first trimester miscarriages, polycystic ovaries, and hypersecretion of luteinising hormone.

Interventions—Women were randomised before conception to receive pituitary suppression with a luteinising hormone releasing hormone analogue followed by low dose ovulation induction and luteal phase progesterone (group 1) or were allowed to ovulate spontaneously and then given luteal phase progesterone alone or luteal phase placebo alone (group 2). No drugs were prescribed in pregnancy.

Main outcome measures—Conception and live birth rates over six cycles.

Results—Conception rates in the pituitary suppression and luteal phase support groups were 80% (40/50 women) and 82% (46/56) respectively (NS). Live birth rates were 65% (26/40) and 76% (35/46) respectively (NS). In the luteal phase support group there was no difference in the outcome of pregnancy between women given progesterone and those given placebo pessaries. Live birth rates from an intention to treat analysis were 52% (26/50 pregnancies) in the group given pituitary suppression and 63% (35/56) in the controls (NS).

Conclusions—Prepregnancy suppression of high luteinising hormone concentrations in ovulatory women with recurrent miscarriage and hypersecretion of luteinising hormone does not improve the outcome of pregnancy. The outcome of pregnancy without pituitary suppression is excellent.

Introduction

Hypersecretion of luteinising hormone is strongly associated with subfertility and early pregnancy failure. Studies from assisted conception cycles have shown an adverse effect of high luteinising hormone concentra-

tions on fertility¹⁻³ and early pregnancy outcome.^{4,5} A similar effect has been reported in spontaneous, unstimulated cycles.^{6,7} Women with a history of recurrent early miscarriage have a high prevalence of polycystic ovaries,^{8,9} and many of these women hypersecrete luteinising hormone.^{10,11}

Endogenous luteinising hormone secretion can be suppressed with agonist analogues of luteinising hormone releasing hormone. Luteinising hormone releasing hormone analogues are used routinely in in-vitro fertilisation treatment protocols with a reported decrease in the number of cancelled cycles, improved pregnancy rates,¹²⁻¹⁴ and a reduction in the number of early miscarriages¹⁵⁻¹⁸ when compared with conventional superovulation techniques. Prepregnancy treatment with luteinising hormone releasing hormone analogues may improve the outcome of pregnancy in women with recurrent miscarriage who hypersecrete luteinising hormone. We evaluated this hypothesis in a randomised controlled trial.

Patients and methods

TRIAL DESIGN

The trial was designed to determine whether pituitary suppression of high endogenous luteinising hormone concentrations followed by low dose ovulation induction and luteal phase progesterone support improves the outcome of pregnancy in ovulatory women with recurrent miscarriage, polycystic ovaries, and hypersecretion of luteinising hormone. To exclude any possible benefit of luteal phase progesterone support the control groups comprised two groups of women who ovulated spontaneously receiving either luteal phase progesterone alone or luteal phase placebo. Women were randomised to receive pituitary suppression (group 1) or luteal phase support alone (group 2) by means of a computer generated random number list (Systat 5.2.1; Macintosh). Women allocated to receive luteal phase support were further randomised by numbered opaque sealed envelopes to receive either luteal phase progesterone (subgroup 2a) or luteal phase placebo (subgroup 2b). Randomisation to groups 1 and 2 could not be blinded as the clinical effects of pituitary suppression could not be concealed from either the subject or the observer. Allocation to subgroups 2a and 2b was double blind. The main outcome measures were conception and live birth rates over six cycles.

ENTRY CRITERIA

All couples attending the recurrent miscarriage clinic were investigated according to our protocol.¹¹ The trial began in 1992 and women were considered eligible if they

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fulfilled the following criteria: three or more consecutive first trimester miscarriages; age less than 38; spontaneous ovulatory cycles (mid-luteal phase serum progesterone concentration ≥ 30 nmol/l); no involuntary delay of more than 24 months in conceiving previous pregnancies; body mass index (weight (kg)/height(m)²) 19-25; polycystic ovaries seen on pelvic ultrasound¹⁹; mid-follicular phase serum luteinising hormone concentration ≥ 10 IU/l or increased urinary luteinising hormone excretion, or both; mid-follicular phase serum follicle stimulating hormone concentration < 10 IU/l; normal uterine morphology seen on pelvic ultrasound; normal karyotype of woman and partner; negative screening test result for phospholipid antibodies (lupus anticoagulant and anticardiolipin).

ASSAYS

Serum luteinising hormone, follicle stimulating hormone, and β human chorionic gonadotrophin concentrations were measured with Abbott's reagents in the IMx microparticle enzyme immunoassay (Abbott Diagnostics Ltd, Maidenhead, Berkshire). Serum testosterone and progesterone concentrations were measured by enzyme linked immunosorbent assay (ELISA) with the ES 300 (Boehringer, Lewes, East Sussex). We find that daily urinary luteinising hormone measurements are a more sensitive method of detecting hypersecretion of luteinising hormone than a single follicular phase serum luteinising hormone measurement.¹⁰⁻¹¹ Aliquots of early morning urine were assayed daily for luteinising hormone over the course of a complete menstrual cycle with the Chelsea luteinising hormone rapid radioimmunoassay kit (Department of Biochemical Endocrinology, Hammersmith Hospital, London). Raised secretion of luteinising hormone was defined as two or more measurements above 100 IU/l before day minus 3 or after day 4 relative to the mid-cycle luteinising hormone peak.¹⁰

TREATMENT PROTOCOLS

Group 1

Women in group 1 began pituitary suppression with the luteinising hormone releasing hormone analogue buserelin (Suprefact) 1200 μ g/day intranasally within five days after the onset of menstruation. Buserelin was continued without interruption until either pregnancy was confirmed or six consecutive cycles had been completed. When serum luteinising hormone concentrations were suppressed to less than 2 IU/l and ultrasound scanning showed the endometrium to be less than 5 mm thick with no ovarian follicles greater than 10 mm diameter ovulation induction was begun with a low dose protocol. The low dose stepwise regimen developed in our centre is aimed at producing a single dominant follicle with a resultant low incidence of multiple pregnancies and ovarian hyperstimulation.⁵⁻²⁰

Human menopausal gonadotrophin (Normegon) was begun at 52.5 IU intramuscularly daily for up to two weeks. When required the dose was increased to 75 IU daily and thereafter was increased in weekly increments of 37.5 IU until a dominant follicle developed. Human chorionic gonadotrophin (Profasi) 5000 IU intramuscularly was given to induce follicle rupture when the dominant follicle had reached a mean of at least 18 mm diameter. Cycles in which more than two dominant follicles developed were abandoned. The luteal phase was supported with progesterone pessaries (Cyclogest) 400 mg per vaginam twice daily for 10 days begun three days after the dose of human chorionic gonadotrophin. A serum β human chorionic gonadotrophin pregnancy test was performed if no menstruation occurred by 18 days after the dose of human chorionic gonadotrophin.

Group 2

Women in group 2 had their cycles monitored by ultrasound until a dominant follicle developed. No

pituitary suppression or ovulation induction was given. Three days after ovulation either progesterone pessaries 400 mg twice daily (subgroup 2a) or placebo pessaries (subgroup 2b) were given per vaginam for 10 days. A maximum of six cycles were monitored and a serum β human chorionic gonadotrophin pregnancy test performed if menstruation was delayed by three days.

MONITORING IN PREGNANCY

A pelvic ultrasound scan was obtained three weeks after ovulation followed by weekly ultrasound scans until 12 weeks' gestation, when antenatal care was arranged. Women were followed up until the end of the pregnancy (either miscarriage or live birth).

POWER CALCULATIONS AND STATISTICAL ANALYSIS

The reported risk of miscarriage after three consecutive losses varies between 20% and 70%.²¹ Most studies have been retrospective but one prospective study showed the risk of a further miscarriage after three consecutive losses to be 43%.²² However, in the presence of luteinising hormone hypersecretion the risk of miscarriage is reportedly as high as 65%.⁶ We therefore assumed a live birth rate of 50% in the control groups and considered that an improvement to 75% in the group given pituitary suppression would be clinically significant. We calculated that 176 pregnancies (88 in group 1, 44 in each of subgroups 2a and 2b) were needed to achieve a study power of 80% to find a difference of this magnitude to be significant at the 5% level. For ethical reasons we performed an interim analysis when the outcome of pregnancy in 86 women suggested that treatment group 1 was not different from treatment group 2. Statistical analysis was by the χ^2 and Mann-Whitney U tests.

ETHICAL APPROVAL

The trial was approved by the St Mary's Hospital Medical School local research ethics committee. All women gave written informed consent before the study.

Results

Between February 1992 and May 1995, 106 women were recruited. Women randomised to group 1 (pituitary suppression) and group 2 (luteal phase support) were well matched for age, number of miscarriages, obstetric history, and conception rate (table 1). Most women had increased urinary excretion of luteinising hormone in both the follicular and luteal phases of the cycle (table 1). Ten women in group 1 (20%) and 12 in group 2 (21%) had follicular phase serum luteinising hormone concentrations ≥ 10 IU/l. Four women in group 1 (8%) and nine in group 2 (16%) had serum testosterone concentrations ≥ 3 nmol/l.

Eighty six women conceived within six cycles. The number of conceptions was similar in women who received pituitary suppression (40/50; 80%) and women who did not (46/56; 82%) ($P=0.78$). Sixteen women completed their designated treatment but failed to conceive in six cycles and a further two women in each group discontinued treatment (one marital breakdown, three unable to cope with the treatment or number of visits). There was no significant difference in age, pretrial follicular phase serum luteinising hormone concentrations (median concentrations 6.3 and 7.5 IU/l respectively), and serum testosterone concentrations (median concentrations 2.1 and 1.9 nmol/l) between women conceiving in the trial and those completing treatment but not conceiving.

Table 2 gives the details of the 86 pregnancies. Women given pituitary suppression had significantly lower follicular phase serum luteinising hormone concentrations after treatment than women who were not suppressed. There was no significant difference in the number of live births

between women who conceived in group 1 (26/40; 65%) and those who conceived in group 2 (35/46; 76%) (difference 11%; 95% confidence interval 8% to 30%). The outcome of pregnancy was not different when the luteal phase was supported with progesterone or placebo (16/20 (80%) *v* 19/26 (73%); difference 7% (31% to 18%). Comparison between group 1 and subgroups 2a and 2b separately also showed no significant difference in the number of live births (table 2). Intention to treat analysis showed no significant difference in the number of live births after randomisation to group 1 (26/50; 52%) compared with group 2 (35/56; 63%) (difference 11%; 8% to 29%).

Further analysis of the subgroup of women who had a raised follicular phase serum luteinising hormone concentration in addition to increased urinary luteinising hormone excretion showed no apparent benefit from pituitary suppression. The live birth rate from intention to treat was 40% (4/10 women) in group 1 and 67% (8/12) in group 2 (*P*=0.4).

No ectopic pregnancies, late miscarriages, or stillbirths occurred during the trial. Pituitary suppression and ovulation induction led to three twin pregnancies, all of which resulted in live births. Of the singleton pregnancies, the mean gestation at delivery was 38.7 weeks in group 1 and 39.2 weeks in group 2. The mean gestation at miscarriage was 8.4 weeks in group 1 and 8.7 weeks in group 2. The proportions of anembryonic pregnancies in the two groups were 40% and 45% respectively. In all the remaining cases fetal heart activity was documented before miscarriage.

Discussion

So far as we know this is the first trial of luteinising hormone suppression in ovulatory women with a history of recurrent miscarriage and high luteinising hormone concentrations. Suppressing endogenous luteinising hormone secretion did not improve the con-

ception or live birth rate in these women. Other workers report that improved pregnancy and live birth rates can be achieved by in vitro fertilisation and ovulation induction regimens that include pituitary suppression.¹⁵⁻¹⁸ Their data, however, were mainly retrospective, and care must be taken when attempting to extrapolate data from subfertile women having assisted conception to a different population of women.

This trial employed strict entry criteria in order to exclude other known causes of recurrent miscarriage, and only ovulatory women were included. From our database of 1500 consecutive cases of recurrent miscarriage we find that over 80% of women with polycystic ovaries have regular menstrual cycles and are therefore likely to be ovulatory.

After 106 women had been recruited to the trial it was evident that there was a high live birth rate in the controls. This prompted an interim statistical analysis, which showed that pituitary suppression could at best result in only an 8% improvement and at worst lead to a 30% reduction in the live birth rate as compared with controls. We concluded that this effect was not clinically useful. As we could no longer justify such an intensive treatment for recurrent miscarriage the trial was stopped.

The mechanism or mechanisms underlying the reported association of hypersecretion of luteinising hormone with subfertility and miscarriage¹⁻⁷ remain unclear. Several workers have suggested that inappropriately high luteinising hormone concentrations in the follicular phase of the cycle cause premature resumption of meiosis leading to the release of a "prematurely aged" oocyte.^{1-4 23 24} Luteinising hormone receptors have been identified in the endometrium,²⁵ raising the possibility of a direct action of luteinising hormone at this site. Our results suggest that luteinising hormone is a downstream marker of some other endocrinopathy associated with polycystic ovaries, as suppression of endogenous luteinising hormone secretion did not lead to an

Table 1—Characteristics of women recruited to trial

	Group 1 (pituitary suppression) (n = 50)	Group 2 (luteal phase support) (n = 56)	Subgroup 2a (progesterone) (n = 25)	Subgroup 2b (placebo) (n = 31)
Mean age (years) (SD)	31 (4)	31 (4)	31 (4)	32 (4)
Median No of miscarriages (range)	4 (3-10)	4 (3-9)	4 (3-9)	4 (3-6)
No (%) with previous live births	17 (34)	20 (36)	10 (40)	10 (32)
Urinary luteinising hormone excretion:				
No (%) with increased excretion in follicular and luteal phases	32 (64)	40 (71)	18 (72)	22 (71)
No (%) with increased excretion in follicular phase only	10 (20)	8 (14)	5 (20)	3 (10)
No (%) with increased excretion in luteal phase only	8 (16)	8 (14)	2 (8)	6 (19)

Table 2—Details of pregnancies

	Group 1 (pituitary suppression) (n = 50) (A)	Group 2 (luteal phase support) (n = 56) (B)	Subgroup 2a (progesterone) (n = 25) (C)	Subgroup 2b (placebo) (n = 31) (D)	
No (%) of mothers who conceived in six cycles	40 (80)	46 (82)	20 (80)	26 (84)	(A) <i>v</i> (B) : <i>P</i> =0.78 †
Median No of cycles to conception	2	2	1	3	
Median conception cycle mid-follicular phase luteinising hormone concentration (IU/l) (range)	1.4 (1.0-4.8)	5.9 (2.8-14.0)	5.6 (2.8-14.0)	4.8 (2.9-14.0)	(A) <i>v</i> (B) : <i>P</i> <0.001‡
Median conception cycle mid-luteal phase luteinising hormone concentration (IU/l) (range)	1.0 (1.0-2.0)	2.4 (1.0-12.0)	2.4 (1.0-11.0)	1.8 (1.0-12.0)	(A) <i>v</i> (B) : <i>P</i> <0.001‡
No (%) of live births	26/40 (65)§	35/46 (76)	16/20 (80)	19/26 (73)	(A) <i>v</i> (B) : <i>P</i> =0.26 † (A) <i>v</i> (C) : <i>P</i> =0.37 † (A) <i>v</i> (D) : <i>P</i> =0.49 †
No (%) of live births from intention to treat analysis	26/50 (52)	35/56 (63)	16/25 (64)	19/31 (61)	(A) <i>v</i> (B) : <i>P</i> =0.27 † (A) <i>v</i> (C) : <i>P</i> =0.32 † (A) <i>v</i> (D) : <i>P</i> =0.41 † (C) <i>v</i> (D) : <i>P</i> =0.84 †

† χ^2 test.

‡ Mann-Whitney U test.

§ Includes three twin pregnancies.

Key messages

- Pituitary suppression of high luteinising hormone concentrations does not improve the outcome of pregnancy in women with a history of recurrent miscarriage
- Hypersecretion of luteinising hormone seems not to be causally related to early pregnancy loss
- Further research should be directed at other endocrine factors controlling implantation
- Excellent live birth rates can be achieved with supportive care alone in a specialised clinic

improved rate of conception or live births. Attention must now be directed at other endocrine factors that govern implantation and in particular at how this process is defective in women with recurrent miscarriage.

Our results emphasise the importance of supportive care in early pregnancy. All groups of women were seen regularly by a specialist team both preconceptionally and throughout the first trimester. Other studies have noted the beneficial effect of "tender loving care" on the outcome of pregnancy.^{26 27} We have recently reported that supportive care in early pregnancy is the most important factor in determining the outcome in women with a history of unexplained recurrent miscarriage.²⁸ Pituitary suppression and ovulation induction is a time consuming, expensive, and stressful treatment that has potentially serious medical complications. Our data show that luteinising hormone suppression before conception does not improve the outcome of pregnancy in ovulatory women with recurrent miscarriage who hypersecrete luteinising hormone. The live birth rate of 76% in the controls emphasises the value of thorough investigation and supportive care of women with recurrent miscarriage in a dedicated miscarriage clinic.

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ONE HUNDRED YEARS AGO

The embarrassment of Guy's Hospital

The authorities of Guy's Hospital are now making a determined attempt to raise a sum of £500,000 for investment, to make good the depreciation in income from the endowment, which almost wholly consist of agricultural property. That an appeal from a great institution like Guy's is a matter of national importance is evidenced by the warm interest which the Prince of Wales is taking in the movement for re-endowment, and H.R.H. will preside on May 20th next at the only festive dinner ever held in connection with this hospital. A feature of the movement of much interest, more especially

to the medical profession, is the manner in which old Guy's men and present students are rallying to the support of their Alma Mater. Already Guy's men in practice have influenced several munificent donations, while it is believed that the majority are doing something. The present members of the Medical School have voluntarily organised themselves into a collecting committee, and, if Providence helps those who help themselves, then it may safely be prophesied that Guy's Hospital will not only maintain its present position, but also reopen its closed beds. (*BMJ* 1896;i:682.)