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Pertubation with Lignocaine – a Possible New Treatment for Women with Endometriosis and Impaired Fertility

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ABSTRACT

The causal relationship between reduced fertility and early stage endometriosis without pelvic adhesions is unclear. Peritoneal fluid from patients with endometrial peritoneal implants contains more leukocytes with an increased capacity to phagocytose spermatozoa. Peritoneal fluid supplemented with lignocaine has a reduced sperm phagocytosis capacity. The present clinical study with low-dose lignocaine pertubation sought to evaluate any clinical effect on fertility. An overall pregnancy rate of 30% was noted in contrast to the natural pregnancy rate for women with endometriosis which is <5%. To confirm these findings a larger study and further dose-ranging are in progress. Up to now the most effective way of increasing fertility for women with endometriosis or unexplained infertility is in vitro fertilisation (IVF). The pertubation treatment with lignocaine is inexpensive and less invasive. Its mechanism is thought to be reduced phagocytosis of the spermatozoa. Another explanation could be a regressive effect directly on the endometriotic implants, taking into account the reduced menstrual pain and increased pregnancy rate after all treatments have been completed. The finding may provide a minimal invasive and more cost-effective alternative to current treatments.

INTRODUCTION

Women with endometriosis suffer from reduced fertility and various degrees of dysmenorrhoea [3, 4]. Despite previous investigations the causal relationship between reduced fertility and endometriosis without pelvic adhesions is not clear and neither is the lack of an improved fertility rate after treatment [8]. There are more leukocytes in the peritoneal fluid from patients with endometrial peritoneal implants, which has been

considered an ongoing sterile inflammation [2,7]. These leukocytes constitute in vivo-primed macrophages which secrete a macrophage-derived growth factor (MDGF) and this may explain the proliferation of the endometrial tissue [5]. Other secretory products from the macrophages, growth factors such as tumour necrosis factor TNF and interferon, exhibit gamete toxicity and may also have an adverse effect on the fertility process [6]. Cell-free peritoneal fluid significantly reduces the capacity of the fimbriae to pick up the fertilised ovum [17]. This finding may also be important for the lower fecundity in patients with endometriosis. In addition, the progressive velocity of spermatozoa is lower in peritoneal fluid from patients with endometriosis and unexplained infertility [13]. Peritoneal fluid macrophages in women with endometriosis may also have an increased capacity to resist apoptosis and the continued survival of the leukocytes might be crucial for fertility [9, 10]. Further, phagocytosis of spermatozoa was increased during incubations for 24 h in vitro with peritoneal fluid from patients with endometriosis [12].

An in vitro study was undertaken to further analyse spermatozoa-leukocyte interaction in patients with endometriosis in search of a potential therapeutic approach. Phagocytosis and sperm viability were assessed during incubations in peritoneal fluid from healthy women and women with endometriosis. To exclude immunological influences, only one sperm donor participated. The incubations with peritoneal fluid were carried out with or without the supplementation of lignocaine, which was chosen for its documented cell membrane-stabilising effect [11]. Lignocaine had no effect on the spermatozoa alone in the cell medium but the number of free spermatozoa, not adhered to leukocytes, was significantly greater in the human peritoneal fluid incubations supplemented with lignocaine [1] . It was concluded that lignocaine could contribute to increasing the number of free spermatozoa in vitro and hopefully in vivo increasing the possibility of fertilising an oocyte.

In vivo evaluation was carried out during 1998-1999 in a clinical study with low-dose lignocaine pertubation. Lignocaine has been used for many years with no reports of adverse effects during pregnancy [15, 18]. Pertubation alone increases the pregnancy rate to 7 % in women with unexplained infertility [19]. The objective of the present study was thus to evaluate the clinical effect on fertility when lignocaine is added to peritoneal fluid pre-ovulatorily in women with early-stage endometriosis and impaired fertility.

METHODS

Patients with a peritoneal or ovarian endometriosis and at least one year's primary or secondary infertility were offered participation in the study. The inclusion criteria were that a previous basic infertility investigation of the couples participating had demonstrated normal conditions concerning ovarian function, negative Chlamydia test, absence of bacterial vaginosis, normal fallopian tubes, normal sperm count and postcoital test. At the time of the previous laparoscopy, there were no adhesions or endometriomas. The first 30 patients to accept (age 26-44 years, mean age 34 years) were included in the study. The clinical routine gynaecological examination including ultrasound examination was also normal prior to each treatment. All patients participating gave their informed consent.

Each patient received three Ringer and three Ringer-lignocaine pertubations (0.1 mg lignocaine/ml), thus in total six treatments blindly alternating with or without lignocaine. The pertubations were given the same day as the pre-ovulatory LH peak value, which was diagnosed by testing in urine samples. A small thin catheter for hysterosonosalpingography (Schering AG) was inserted in the uterine cavity and the small intraluminal rubber balloon on the catheter was inflated with saline to prevent retrograde leakage. 10 ml solution was infused through the uterine cavity and pertubated into the peritoneal cavity. No pressure was used for the pertubation procedure, since a prerequisite for participation was patent fallopian tubes. After the pre-ovulatory pertubation treatment the couple tried to achieved pregnancy by coitus. For patients where scheduled marital life was a temporary problem, occasional insemination was offered the day after pertubation. The results of the treatment were measured by the pregnancy rate defined as any increase of serum HCG level or ultrasound-verified intrauterine pregnancy. The procedure was approved by the local ethics committee and the Swedish Medical Pharmacological Association.

After treatments had been completed the patients answered a questionnaire concerning any change in dysmenorrhoea and pre menstrual syndrome (PMS) and questions covering the need for pharmacological treatment and/or sick-leave before and after the pertubation treatments.

RESULTS

An overall pregnancy rate of 30% was found in this limited group of 30 participants. The occurrence of pregnancies (n=9) was registered during the six pertubation cycles or within

one year after the treatments were completed. The patients (n=12) who received fewer than six treatments discontinued their treatment because of normal pregnancy (n=4, mean age 34 years), offers of treatment from the IVF waiting list (n=2) or because the pertubation treatment was unpleasant physically (n=5) or psychologically (n=1). The babies were all healthy (n=5) and included one twin pregnancy. Pregnancies ending in early spontaneous abortion (n=5, mean age 34 years) were not more numerous than could be expected.

Two pregnancies occurred during cycles where lignocaine was given, another two during cycles where pertubation with Ringer solution alone and the remaining 5 after all six treatments or during cycles where treatment was omitted due to e.g. holiday. However, during the treatments a few patients reported spontaneous regression of dysmenorrhoea and PMS symptoms. When this was further investigated with questionnaires, reduced dysmenorrhoea was found in 32 % (n=8) of those patients suffering from dysmenorrhoea (n=25). Among the patients with PMS (n=20) 30 % reported (n=6) alleviation after finishing pertubation treatment.

DISCUSSION

For patients with endometriosis, pertubation treatment with lignocaine might be a means of increasing the chances of conception. The present clinical study sought to evaluate in vivo any positive fertility effect of lignocaine [1]. The purpose was also to investigate whether the pertubation method could be used as an alternative to assisted fertilisation such as IVF (in vitro fertilisation). During this clinical study for the treatment of infertility in the endometriotic patient, pertubations were carried out pre-ovulatorily with Ringer solution with or without lignocaine supplementation. The pregnancies noted in the present participants is encouraging but not conclusive enough to draw any definite conclusions. Pertubation itself such as is carried out during X-ray examination of the fallopian tubes will given a pregnancy rate of 7 % [19] in patients with unexplained infertility. The spontaneous pregnancy rate for women with endometriosis is <5 % [4]. The overall pregnancy rate of 30 % in this clinical study matches that of IVF and is higher than the spontaneous expected rate after pertubation. The pregnancies ending in spontaneous abortions are the expected incidence for this age group. We expected the lignocaine pertubation treatment to reduce phagocytosis of the spermatozoa, but this did not seem to

be the main effect in this study. An alternative explanation could be regression of endometriosis, taking into account the reduced menstrual pain and increased pregnancy rate after the initial six treatments had been completed. For those who noticed reduced dysmenorrhoea but did not become pregnant, the reduced pain level lasted around one year. It is too early to evaluate the "take-home baby rate" in comparison to IVF. The lignocaine pertubation treatment could be an alternative prior to IVF treatment or when IVF is prohibitive in terms of cost, age or medical resources.

About half of all women suffer from dysmenorrhoea [14] and 30-80 % have problems with PMS [16]. The patients who reported reduced symptoms of endometriosis such as dysmenorrhoea or became pregnant after all treatments had been given, raise the question of whether lignocaine could have a direct effect on the endometrial implants. In the continued double-blind study now in progress, the patients will be randomised to Ringer solution with or without supplementation of lignocaine. The results of will be used to establish whether the lignocaine supplementation can reduce dysmenorrhoea and increase the pregnancy rate more than Ringer pertubation without lignocaine.

In conclusion, this study imply a possible new treatment but the mechanism of the effect on fertility, dysmenorrhoea and PMS is unclear. The expectation was to reduce the phagocytosis of spermatozoa described during endometriosis, however, effect on other peritoneal factors could be involved. The most effective way of increasing fertility for women with endometriosis has been in vitro fertilisation (IVF), a treatment that is time-consuming, expensive and for some couples physically and psychologically traumatic. The pertubation treatment described in this article, is less invasive and less expensive (less than 10% per cycle compared to a full IVF treatment cycle). Further studies may provide the scientific data necessary to formulate a less invasive and more cost effective-alternative to current modalities of treatment. To evaluate these preliminary findings a larger clinical study is in progress including further dose-ranging.

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