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Indomethacin effect on implantation rates in oocyte recipients

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BACKGROUND: Implantation failure is the main limiting factor for success of IVF. Even when transfer techniques are carried out extremely carefully, embryo transfer may produce an endometrial and cervical reaction that may result in an inflammatory response and impaired implantation. There are no formal specifications on the use of indomethacin in reproductive cycles and there are no studies published in the scientific literature on its effect on embryo implantation. Oocyte donation is the best model to evaluate the determinants of implantation. The aim of this study is to evaluate the potential benefit of indomethacin administered at embryo transfer. METHODS: A randomized pilot trial of 136 oocyte recipients was carried out. Seventy-two women received standard specifications plus 100 mg of indomethacin rectally given as three doses every 12 h starting on the night prior to transfer. RESULTS: Positive HCG (>= 6mUI/ml) occurred in 59.7% of treated women and in 59.4% of women in the control group. Implantation rates were 27.8% in the indomethacin group and 26.4% in the controls. CONCLUSIONS: The indomenthacin group did not show significantly higher implantation rates. A larger study exploring alternative treatment protocols might be appropriate.

Key words: embryo transfer/endometrial receptivity/implantation/randomized pilot study

Introduction

Implantation failure is the main limiting factor for success in IVF in reproductive medicine. As an aggressive procedure, embryo transfer provokes a uterine response involving endometrial inflammatory phenomena and increased myometrial activity. Factors that may induce a uterine response include hyperphysiological hormonal levels, direct myometrial effects of the drugs used in the cycles, local inflammatory responses due to external particles introduced by manipulation, dynamic responses due to stimulation of the cervix and intracavitary canalization, the stress experienced by a woman who is undergoing a reproductive cycle, or unknown causes.

Uterine activity is well established (Ijland *et al*., 1996; Van Gestel *et al*., 2003). Since the introduction of IVF, an increased uterine activity was also documented, as well as its harmful effects on embryo attachment (De Vries *et al*., 1990; Ijland *et al*., 1998, 1999; Bulleti *et al*., 2000) and a high number of embryos ejected (Menezo *et al*., 1985; Poindexter *et al*., 1986). During mock embryo transfers, a tenaculum applied to the cervix elicited the release of oxytocin and increased uterine contractions (Lesny, 1999).

Therefore, even when transfer techniques are carried out extremely carefully, embryo transfer may produce an inflammatory response and/or increased contractility, which may result in implantation failure. Due to the close relationship and interaction between the endometrium and myometrium, we cannot consider the uterus as a passive container. Although, for obvious reasons, we cannot study the immediate endometrial response in humans after the embryo transfer, it may be hypothesized that factors related to a decreased uterine activity and inflammatory endometrial response at the moment of embryo transfer might increase the chances of embryo implantation. Until recently, little attention has been paid to the role of embryo transfer techniques (Englart *et al*., 1986; Mansour *et al*., 1990; Mansour *et al*., 2002) and even less to its pharmacological management (Kovacs, 1999).

Indomethacin, a non steroidal anti-inflammatory drug (NSAID), widely used in clinical practice, has well known anti-prostaglandin effects that reduce uterus contractility. It also has vasodilatory action (Hiemeyer, 1967; Saksena, 1974; Lau, 1973). Its uterolytic effects in gravid uterus are well known, as well as its benefits in treating dysmenorrhoea.

We also know that the production of inflammatory cytokines is important for successful implantation, but excessive production may be detrimental (Chaouat *et al*., 2002). In addition to the exogenous manipulation, introducing extrauterine particles (cervical mucus, bacteria, detritus, and so on) could trigger a ‘pro-inflammatory status’ (Chaouat *et al*., 2002). Nonetheless, in 4 day pregnant rats, intrauterine indomethacin at moderate or low doses did not show any anti-implantation effects (Gupta

et al., 1981). Furthermore, indomethacin has been used successfully in animal models to reduce the anti-implantation effect of intrauterine devices (Chaudhury, 1975; Hurst *et al*., 1982). However, there are no studies published on the effect of indomethacin on human embryo implantation, and no formal specifications for its use in reproductive cycles.

Oocyte donation is the best model to evaluate the determinants of implantation, for several reasons. First, there is a minimal variability in embryo quality, as donors are young women of a similar age with no ovulatory disorders. Secondly, the preparation of the endometrium is similar, as all recipients receive the same hormonal replacement protocol. Finally, as procedures are performed under the same circumstances and by the same medical team, the embryo transfer techniques are similar for all participants. Therefore, in spite of being fully allogenic, embryos transferred in oocyte donation programmes have relatively high implantation rates.

The objective of the study was to assess whether indomethacin has a positive effect on implantation rates using an oocyte recipient model. The specific hypothesis of the study was that indomethacin would improve oocyte implantation rates.

Subjects and methods

Selection of the subjects

An ongoing randomized clinical trial of 173 first cycle oocyte recipients following IVF and ICSI was established in June 2003. A random sequence of 173 treatment and control codes was generated by the epidemiologist and written in a table, in which each cell had one number (from 1 to 100) and one treatment (A) or control (B) code. The gynaecologist specially assigned to attend recipients was instructed to assess inclusion and exclusion criteria and was responsible for including women in the study and for writing the medical history number of the women in the table. Once all 100 code numbers had been allocated, the allocation sequence was restarted at number 1.

Women who approached the clinic for IVF or ICSI and were willing to collaborate and eligible for inclusion were randomly assigned to either the intervention or control group by their attending gynaecologist on the day of their first visit. Women were informed of the objectives of the study and their consent was obtained before proceeding. The table with the codes and medical history numbers remained with that gynaecologist throughout the study. Patients who were in the control group did not receive a placebo.

Once reproductive cycles were completed for all women, the data from the medical history were written onto a database by a biologist blind to the treatment or control code of the patient. Women included in the study were later identified using their medical history numbers and their corresponding codes for treatment or control included in the database. Therefore, the clinical staff that performed the transfer and assessed study outcomes were blind to whether the women were in the treatment or control groups.

Inclusion criteria were: (i) first cycles of women candidates to be oocyte recipients (IVF and ICSI); (ii) no known allergic reaction to NSAIDs and; (iii) no neurological or gastrointestinal disease. Exclusion criteria for recipients were: (i) recurrent miscarriage; (ii) endometrial pathology; and (iii) severe endometriosis.

Baseline variables were obtained in all women on their visit to the clinic. Information on possible confounders, age of recipient and donating women, endometrial thickness, type of endometrial line, semen quality, oocyte quality, number of embryos transferred, embryo quality, and quality of transfer was determined in all women. To reduce variability in oocyte quality, all donors were young (mean age 26.2±0.4 years) with normal body mass index (BMI) and no ovulatory disorders (normal baseline hormonal levels and normal ovarian ecography). All donors received the same induction protocol using rFSH (Gonal F; Laboratorios Serono, Madrid, Spain) under LHRH analogue suppression in a short protocol (Procrin; Abbott Laboratories, Madrid, Spain). This study was approved by the ethical and research committee of the Institute. The study design is presented in Figure 1.

Intervention protocol

Standard specifications for oocyte recipients included a standard protocol of ethynyl-estradiol transdermal patches with increasing doses starting at 50 mg daily from day 1 to 7, (Dermestril, Laboratorios Rottafharm, Barcelona, Spain), 100 mg daily from day 8 to 11, and 150 mg from day 11 onwards, plus intravaginal micronized progesterone (Utrogestán, Laboratorios Seid, Barcelona, Spain) 200 mg every 8 h starting on the afternoon of the oocyte pick-up and continuing up to the day of β-HCG measurement 11 days later. If the β-HCG result was positive, we maintained the same protocol until the 11th week of pregnancy. The intervention group received standard specifications plus three doses of 100 mg of indomethacin rectally every 12 h, starting on the night prior to the transfer. The non-intervention group received standard specifications only.

Embryo transfer procedure

All transfers were done on days 2 or 3 following the same protocol, with a full bladder, using ultrasound guidance and the same soft catheter (Embryo transfer catheter Rocket Medical, Washington, UK), and performed by the same experienced biologist and medical team. Both, the biologist and the medical team were blind to the status (indomethacin or control group) of the patients.

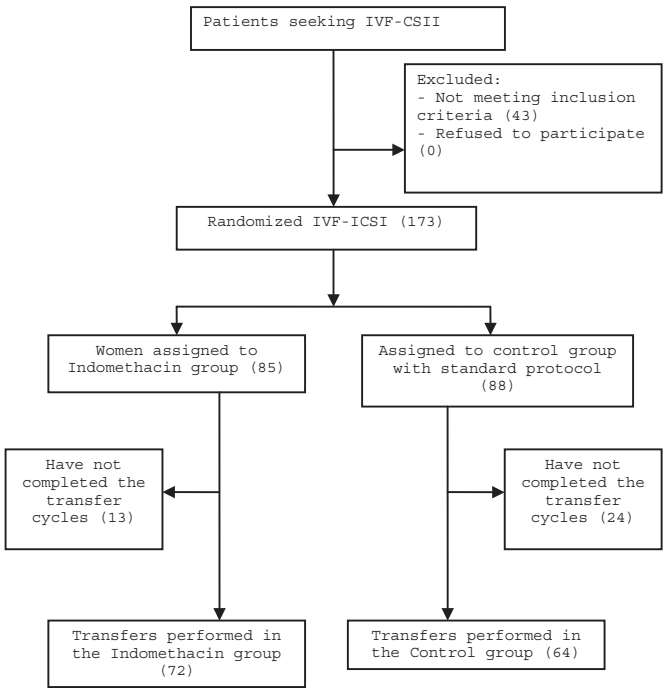

Figure 1. Study design of the randomized pilot study on indomethacin effectiveness for women recipients in an oocytes donation program.

Outcome variables

There were two outcome variables in the study. Biochemical pregnancy is defined as β-HCG >5IU. Implantation is defined as an embryonic sac visible with ecography at day 11 post-transfer in women with a biochemical pregnancy. The implantation rate the main outcome of the study is defined as the ratio between the number of embryonic sacs visible with ecography at day 11 post-transfer in women with a biochemical pregnancy and the number of embryos transferred. Biochemical analyses and ecographies were performed by professionals blind to the indomethacin status of the women, and following standard procedures.

Sample size, data management and analysis

Due to the slow recruiting process involved in identifying suitable oocyte recipients, the study was designed as a concurrent and still ongoing study. We present here the results of the first 136 women who have completed the cycles from the 173 women who were recruited for the study. Data entry was done in SPSS 12 by a member of the staff blind to the objectives and clinical outcomes of the study. In the analyses, we compared the percentages of biochemical pregnancies and implantation in the two groups. Adjustments were made for possible confounders. Crude and adjusted analyses were conducted using SPSS 12.

Results

In total, 173 women were randomly assigned to either group. In 37 women (13 women in the indomethacin group and 24 in the control group) who were recruited into the study, the cycles have not been completed. Consequently, embryo transfers were not performed in those women and analyses were conducted on the women in whom embryo transfer were performed. Baseline variables and possible confounders were similarly distributed in both groups (Table I). The reasons why women were included in the oocyte donation programme are presented in Table II.

Table I. Comparison of baseline characteristics in the intervention and control groups in women who completed the protocol ($n=136$)

	Study groups			
	Indomethacin ($n=72$)		Control ($n=64$)	
	Mean	SE	Mean	SE
Donor's age (years)	25.2	0.5	27.2	0.5
Days of stimulation of donor women	10.2	0.2	10.1	0.2
Recipient's age (years)	38.7	0.5	37.7	0.5
Number of cycles	1.1	0.03	1.1	0.03
Million sperm/ml	44.6	11.2	36.8	4.0
% Progressive motility	47.2	2	51.1	2.8
Days of follicular phase	28.8	1.5	26.7	11.1
Endometrial thickness (mm)	10.6	0.3	11.1	1.3
Plasma estradiol (pg/ml)	4774.6	330.7	4369.5	239.2
Embryos per cycle	7.4	0.5	6.9	0.5
Day of transfer	2.6	0.1	2.6	0.1
Number of embryos transferred	2.6	0.1	2.6	0.1
Quality of embryos transferred	1.6	0.10	1.4	0.1
Quality of transfer*	1.4	0.1	1.4	0.1

*Quality of transfer evaluates the presence of blood or mucous in cervix, number of attempts to transfer, and whether endometrium was or not touched.

Table II. Causes of women's infertility

	Indomethacin		Control	
	n	%	*n*	%
No/unexplained	8	11.1%	9	14.1%
Fallopian tubes	2	2.8%	4	6.3%
Endometriosis	1	1.4%	1	1.6%
Ovarian causes	49	72%	35	60.9%
Any combination of the above	4	5.6%	6	10.9%
Others	5	6.9%	4	6.2%
Total	72	100%	64	100%

The main reason why women were included in the donation programme was ovarian failure.

Clinical outcomes are presented in Table III. It should be noted that no adverse effects due to the use of indomethacin were reported. Out of the 136 women who completed the protocol, 59.7% of those who received indomethacin had positive β-HCG values, while β-HCG was positive in 59.4% of the 64 women in the control group [relative risk (RR)=1.0; 95% confidence interval (CI) 0.5–2.0]. Implantation occurred in 50% of women in both groups.

In total, 187 embryos were transferred in the indomethacin group of which 52 implanted, resulting in an implantation rate of 27.8%. In the control group, 166 embryos were transferred, and the implantation rate was 26.4%. Adjustment for possible confounders did not alter the results. The differences between the two groups were not statistically significant.

Discussion

Several strategies have been proposed in order to improve uterus receptivity at the time the embryo reaches the endometrial cavity and to minimize the uterine activity. Reducing cervical stimulation by a careful technique, non-traumatic pass of the catheter through the uterine cavity, or ecographically guided transfer have all shown a beneficial effect. However, apart from the use of progesterone (Fanchin *et al*., 2001) or ritodrine (Pinheiro *et al*., 2003), a pharmacological approach to embryo transfer has not been considered.

We chose indomethacin for its well known action on the gonadal axis inhibiting the release of LH in the hypophysis, delaying or suppressing ovulation, decreasing the number of oxytocin receptors in the endometrium, and finally decreasing the myometrial activity throughout the cycle. Therefore, two possible sites of action could be hypothesized: in the endometrium by decreasing the inflammatory response due to mechanical manipulation and introduction of foreign particles; and in the myometrium by decreasing its activity.

Myometrial contractions progressively increase in frequency, amplitude and direction of propagation toward the uterine fundus throughout the follicular phase, to reach a maximum during the mid-cycle (Abramoivicz, 1990; De Vries, 1990; Lyons, 1991; Ijland, 1996; Bulleti, 2000). The prostaglandin E concentration measured in the myometrium was found to increase progressively, rising to a peak at the end of the follicular and ovulatory periods, and dropping suddenly after ovulation (Vijayakumar,

Table III. Outcome variables in the 136 women of the indomethacin and control groups in whom embryo transfers were performed

	Indomethacin group ($n=72$)				Control group ($n=64$)			
	n	%	Mean	(SE)	*n*	%	Mean	(SE)
% β-HCG positive	43	(59.7%)			38	(59.4%)		
Plasma β-HCG	43		154.3	(21.9)	40		137.6	(17.8)
Women with one or more embryonic sac	36	(50%)			32	(50%)		
Women with one embryonic sac	23	(31.9%)			21	(32.8%)		
Women with two embryonic sacs	10	(13.9)			10	(15.6)		
Women with three embryonic sacs	3	(4.2)			1	(1.6)		
Average number of embryonic sacs per woman with implantation	36		1.4	(0.1)	32		1.4	(0.1)
Implantation rates	191[a]	(27.8%)			168[a]	(26.4%)		

Differences were not statistically significant.
[a]Total number of embryos transferred.

1981). Uterine contractions are known to affect embryo implantation in animals (Adams, 1980; Liedholm, 1980) and in humans (Fanchin *et al*., 2001). Recently, Maslow and Lyons (2004) have reported a clear inhibitory action of ibuprofen on mid-cycle myometrial contractions. Indomethacin had also been used successfully to reduce uterine contractility (Lenz, 1991).

Physiological implantation is described by apposition, adhesion and trophoblast invasion phases. Apposition requires an inflammatory-type reaction followed by an anti-inflammatory-type reaction. Our results suggest that indomethacin did not affect the initial inflammation-type reaction which is essential for the implantation to occur. Studies using animal models had already indicated that indomethacin did not have deleterious effect on this phase (Gupta *et al*., 1981), and could even reduce the anti-implantation effect of intrauterine devices (Chaudhury, 1975; Hurst *et al*., 1982). However, to our knowledge, this is the first study that shows no adverse effect of indomethacin on human implantation.

In our study, the overall pregnancy rate, plasma β-HCG, implantation rates and the number of sacs were similar in both groups, suggesting that there was no better uterine compliance in the indomethacin as compared with the control groups. The small differences found were not statistically significant. It should be noted, though, that 720 women would have been needed in order to achieve a power of 80% and level of significance of 95% with an estimated implantation rate of 27% in untreated women and an effect associated to indomethacin use of 10%. Therefore, small positive effects of indomethacin cannot be entirely ruled out.

The oocyte donor–recipient model allowed us to minimize other possible confounders related to oocyte quality, causes of infertility and male factors. The main reasons why women entered the oocyte donation programme as recipients were ovarian causes. We may expect that their uterine receptivity status would be quite homogeneous. However, women with other causes (endometriosis, unexplained or others) may have unequal uterine receptivity. In fact, when we compared the intervention and control groups within women with ovarian causes of infertility only, indomethacin seems to improve reproductive outcomes by 10% or more (see Table IV), while in the remaining group of women with causes of infertility other than ovarian, the placebo group was far better off (see Table V). Although the differences are not statistically significant, these results are compatible with indomethacin having a positive effect in women with ovarian causes of infertility, while having no effect (or even a deleterious effect) in women

Table IV. Comparison of outcome variables in both groups of women recipients with underlying ovarian causes (n = 84) as a reason for entering the oocyte donation programme

	Indomethacin group ($n=49$)				Control group ($n=35$)			
	n	%	Mean	(SE)	*n*	%	Mean	(SE)
% β-HCG positive	32	(65%)			18	(51%)		
Plasma β-HCG	32		138	(25.8)	18		101.2	(24.2)
Women with one or more embryonic sac	26	(53%)			15	(43%)		
Average number of embryonic sacs per woman with implantation	26		1.5	(0.1)	15		1.3	(0.1)
Implantation rates	128	(29.2%)			89	(21%)		

Differences were not statistically significant.

Table V. Comparison of outcome variables in both groups in women recipients with other that ovarian causes ($n = 52$) as a reason for entering the oocyte donation programme

	Indomethacin group ($n = 23$)				Control group ($n = 29$)			
	n	%	Mean	(SE)	*n*	%	Mean	(SE)
% β-HCG positive	11	(47.8%)			20	(69%)		
Plasma β-HCG	11		201.7	(38.7)	20		174	(24)
Women with one or more embryonic sac	10	(43.5%)			17	(58.6%)		
Average number of embryonic sacs per woman with implantation	10		1.4	(0.2)	17		1.4	(0.1)
Implantation rates	63	(21%)			79	(32%)		

Differences were not statistically significant.

with other causes of infertility. Our study design does not allow us to draw conclusions on the basis of within-group comparisons, but it does raise these intriguing hypotheses for future research.

Some limitations of our study should be noted. The study was not blind for the patient or the physician conducting the first evaluation and the recruitment of the patients into the study. Selection bias might, theoretically, have occurred if the attending gynaecologist had selectively assigned patients to one group or another, or excluded them from the study on the basis of criteria other than those established in the research protocol. As the research protocol was strictly followed in the enrolment and assignment phases, we do not believe that selection bias might have had a significant role in this study. Moreover, as the team conducting the laboratory procedures, clinical transfers and evaluation of the results of the transfer were blind to the status of the patients, we feel that significant information bias may have been prevented.

A final consideration is that indomethacin may be useful but at dosages or regimen protocols different from the one we followed. The protocol and/or the dosages we used for administering indomethacin may not have been adequate. It should be noted that there are no formal specifications on the use of indomethacin, and higher doses or longer administrations may be needed to obtain beneficial effects. Additionally, we did not obtain information prior to transfer on whether indomethacin had or not been used. Having done that would have disclosed their status to the team conducting embryo transfer. However, the disadvantage is that we do not know the degree of compliance in the intervention group. Although our clinical experience is that women seeking IVF-ICSI are highly compliant with medical protocols, low indomethacin use may not be entirely ruled out.

A favourable finding of our study is that no adverse effects or reduced implantation rates were found in the indomethacin group, suggesting that indomethacin use does not disrupt human implantation.

An alternative explanation for our findings is that contractility and/or the inflammatory reaction following embryo transfer may not be an important determinant of implantation failure. A larger study exploring alternative treatment protocols and possible differential effects in patient subsets might be appropriate before completely ruling out any positive effects of indomethacin on implantation rates.

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