was implanted into immunodeficient mice and the effect of nimesulide administration was examined. Before drug treatment experiments were performed, anti-human COX-2 antibodies that specifically detected human but not mouse COX-2 were used to demonstrate that nude mouse xenografts contained the human COX-2 immunoreactive protein, and thus were similar to human endometriotic tissue. The species specificity of the antibody was confirmed by positive anti-human COX-2 immunostaining of late secretory phase eutopic human endometrium but not of mouse endometrial tissue. Positive anti-human COX-2 immunoreactivity was detected in xenografts harvested from untreated mice.

Matsuzaki and Canis question whether the dose of nimesulide we used was sufficient to inhibit COX-2 activity in human tissue present in nude mouse xenografts. It is difficult to understand how they can infer that the dose used was insufficient based solely on changes in immunohistochemical staining. As Matsuzaki and Canis acknowledge, levels of immunoreactivity do not reflect enzyme activity. For this reason, COX-2 protein levels were not compared in treated and untreated nude mouse lesions.

Our study did not address the hypothesis that COX-2 inhibitors may regulate COX-2 immunoreactive protein levels. However, untreated nude mouse lesions harvested 7 days after implantation showed strong human COX-2 immunostaining whereas minimal COX-2 immunoreactivity was present in untreated lesions harvested 10 and 14 days after tissue implantation (unpublished data). These findings suggest that mechanisms other than nimesulide treatment down-regulate human COX-2 protein levels in the estrogen-supplemented nude mouse model of endometriosis over a 10–14 day time-period.

As discussed by Hull et al. (2005), the high dose of nimesulide used in nude mouse model experiments (25 mg/kg) is sufficient to reduce markers of COX-2 activity (prostaglandin E2 levels and other inflammatory parameters) in rodent models of inflammation (Gilroy et al., 1998; Gupta et al., 1999). Furthermore, the serum levels of nimesulide in the nude mouse model of endometriosis were similar to those identified in humans after administration of therapeutic doses of nimesulide (Davis and Brogden, 1994). It is likely that if therapeutic serum levels of nimesulide were achieved in women with endometriosis, the effect of nimesulide treatment would be similar to that seen in nude mice (no significant difference in ectopic endometrial lesion size was detected when control and treated groups were compared).

Matsuzaki’s group introduced myometrium-containing uterine fragments into the peritoneal cavity of cycling rats that had a prolonged exposure to celecoxib (Matsuzaki et al., 2004). In the paper by Hull et al. (2005), ectopic human endometrial lesion size was compared in non-cycling estrogen-supplemented nude mice that had received 10 days of high dose nimesulide. It is likely that the difference in outcomes in these two studies is due to differences in the models of endometriosis, the experimental designs and the administered pharmacological agents used.

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M.Louise Hull and D.Stephen Charnock-Jones
Reproductive Molecular Research Group, Department of Pathology, Tennis Court Road, Cambridge CB2 1QP, UK

E-mail: mlh30@cam.ac.uk
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Peripartum cardiomyopathy (PPCM) in both surrogate and biological mother

Sir,

The purpose of this letter is to alert those involved in assisted reproductive technology to consider the possibility that a precipitating factor for PPCM could be transferred, and to encourage further investigation of potential antigens, both infectious and non-infectious, that may initiate PPCM.

The case is described as follows: a surrogate mother was diagnosed with PPCM at term pregnancy. The embryo was received from the commissioning couple for whom the mother was diagnosed with PPCM following the delivery of her first child 5 years previously.

Prior to her surrogate pregnancy, K.L., aged 34 years, had three previous pregnancies, children aged 9, 5 and 2 years. She underwent IVF in July 2003, with two fertilized embryos resulting from oocytes and sperm harvested from the commissioning couple. She had an uneventful pregnancy until the onset of respiratory symptoms, in her 32nd week of pregnancy (NYHA Functional Class II). Diagnostic testing included an echocardiogram which showed left ventricular end-diastolic diameter (LVEDD) of 2.91 cm/m² body surface area (normal < 2.7 cm/m²) and mild global left ventricular dysfunction with ejection fraction (LVEF) of 0.40–0.45 (normal > 0.50). No other causes for heart failure (HF) could be identified. With a diagnosis of stabilized PPCM, she underwent Caesarean section, with the delivery of healthy twins, a female weighing 5 pounds 1 ounce, and a male weighing 3 pounds 7 ounces. Her subsequent recovery was uneventful. Treatment for her PPCM included carvedilol, lisinopril, and enoxaparin (low molecular weight heparin). Six weeks
postpartum her echocardiogram showed improved left ventricular systolic function, with an LVEDD of 2.63 cm/m² and an LVEF of 0.55. Medications were subsequently phased out, but an echocardiogram done 1 year following diagnosis showed an LVEF of 0.45, and treatment with carvedilol and lisinopril was restarted.

The commissioning/biological mother had one previous pregnancy, with vaginal delivery of a healthy female, weight 11 pounds 6 ounces, in 1998. Investigation of mild clinical symptoms of palpitations (NYHA Functional Class II) included echocardiography, leading to a presumptive diagnosis of PPCM 6 weeks postpartum. At diagnosis, LVEF was 0.40–0.45. Five years later, at the time of embryo harvest for use in IVF, she continued to receive treatment with carvedilol. Left ventricular EF 6 years following diagnosis and 1 year following embryo harvest remained at 0.40–0.45. The two mothers are unrelated, and neither has any family history of cardiomyopathies or any previous history of heart disease.

Peripartum cardiomyopathy is a devastating disease whose aetiology is largely unknown. Diagnostic criteria require the onset of heart failure (HF) in the period 1 month prior to delivery to 5 months postpartum in a previously healthy mother for whom no other cause of HF can be determined (Pearson et al., 2000).

In the USA, mothers reported herein the presence of PPCM in both the surrogate and biological mother, strongly suggesting a causal link rather than a purely chance phenomenon. Leading suspects are transmissible agents, both infectious and non-infectious as well as genetic susceptibility factors. In humans, there is abundant evidence linking viral myocarditis to dilated cardiomyopathy and heart failure (Mason, 2003; Pauschinger et al., 2004). In addition, transfer of virus (Takata et al., 2004), cardiac proteins (Li et al., 2004), anti-cardiac protein lymphocytes (George et al., 2004), and cardiac-sensitized antigen-presenting dendritic cells (Eriksson et al., 2003) have all been shown in experimental animals to be capable of causing a myocarditis which may subsequently lead to dilated cardiomyopathy and HF.

The PPCM Research Project has previously reported a very high incidence of this rare disease in rural Haiti (Fett et al., 2002a, b, 2003, 2004). In the Hospital Albert Schweitzer (HAS) District of Haiti, PPCM occurs with an incidence of one case per 300 live births, which is 10 times that of the estimated incidence in the USA. The finding of a lymphocytic myocarditis in some Haitian PPCM patients suggests a possible viral infection as an initiating antigen, although non-viral antigens ultimately leading to an autoimmune myocarditis could also give a similar histological picture. Ongoing investigations include the search for antigens that may initiate an inflammatory (lymphocytic myocarditis) or non-inflammatory cardiomyopathy and subsequent dilated cardiomyopathy.

An hereditary predisposition is also suggested by familial reports of PPCM and by the Haitian series with PPCM in a mother–daughter pair as well as in a sister–sister pair (Fett et al., 2002c). Both environmental and genetic factors could be playing a role. Although there are no major histocompatibility patterns known or studied for PPCM, there are reports of increased HLA-antigen patterns associated with idiopathic dilated cardiomyopathy (McKenna et al., 1997; Murphy, 2003; Taylor et al., 2004).

In monitoring assisted reproductive treatment, the Centers for Disease Control and Prevention (2001) reported a total of 29,344 live-birth deliveries and 40,687 infants resulting from 107,587 assisted reproduction procedures in the USA and US territories in 2001. Of those procedures, 8,592 (8%) used freshly fertilized embryos from donor oocytes, similar to the procedure used in this case report. Outcome analysis by CDC includes pregnancy success per transfer procedure, number of live births, number of singleton births, and number of multiple-birth deliveries.

There are no reports in the medical literature of the development of PPCM in a surrogate mother. An Internet PPCM support group (E-mail: http://www.ppcmsupport.org and E-mail: http://www.amothersheart.net) carries an entry from a 27 year old gravida 3, para 4 surrogate mother who was diagnosed with PPCM 2 weeks following the delivery of twins. The biological mother did not have a history of PPCM.

I conclude by raising the question: could a cardiomyopathy-precipitating antigen be transmitted during the process of harvesting embryos and subsequent IVF? Because of the increasing use of assisted reproduction technologies, it is very important to continue research efforts to better understand potential risks for the sake of both maternal and child health. Continuing investigation of these cases may also help to better understand the pathogenesis of human PPCM.

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Peripartum Cardiomyopathy Support Group. E-mail: http://www.ppcmsupport.org and E-mail: http://www.amothersheart.net.


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James D. Fett
Hôpital Albert Schweitzer, Deschapelles, Haiti
E-mail: jdftlsc@techline.com

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