Preterm birth in twins after subfertility treatment: population based cohort study

Hans Verstraelen, Sylvie Goetgeluk, Catherine Derom, Stijn Vansteelandt, Robert Derom, Els Goetghebeur and Marleen Temmerman

BMJ 2005;331;1173-; originally published online 25 Oct 2005;
doi:10.1136/bmj.38625.685706.AE

Competing interests: None declared.
Ethical approval: Not required.

1 Brostrom A, Stromberg A, Dahlstrom U, Fridlund B. Sleep difficulties, daytime sleepiness, and health-related quality of life in patients with chronic heart failure. *J Cardiovasc Nurs* 2004;19:234-42.
2 Byles JE, Mishra GD, Harris MA, Nair K. The problems of sleep for older women: changes in health outcomes. *Age Ageing* 2003;32:154-63.
3 Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97-111.
4 Holbrook AM, Crowther R, Lotter A, Cheng C, King D. The diagnosis and management of insomnia in clinical practice: a practical evidence-based approach. *CMAJ* 2000;162:206-10.
5 Aparasu RR, Mort JR, Brandt H. Psychotropic prescription use by community-dwelling elderly in the United States. *J Am Geriatr Soc* 2003;51:671-7.
6 Craig D, Passmore AP, Fullerton KJ, Beringer TR, Gilmore DH, Crawford VL, et al. Factors influencing prescription of CNS medications in different elderly populations. *Pharmacoepidemiol Drug Saf* 2003;12:383-7.
7 Barbone F, McMahon AD, Davey PG, Morris AD, Reid IC, McDevitt DG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998;352:1331-6.
8 Neutel CI, Perry S, Maxwell C. Medication use and risk of falls. *Pharmacoepidemiol Drug Saf* 2002;11:97-104.
9 Fleming JAE. Insomnia. In: Gray J, ed. *Therapeutic choices*. Ottawa: Canadian Pharmacists Association, 2003:54-62.
10 Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, NJ: Earlbaum, 1988.
11 Nowell PD, Mazumdar S, Buysse DJ, Dew MA, Reynolds CF 3rd, Kupfer DJ. Benzodiazepines and zolpidem for chronic insomnia: a meta-analysis of treatment efficacy. *JAMA* 1997;278:2170-7.
12 Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, et al. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry* 2002;159:5-11.
13 Holbrook A, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ* 2000;162:225-33.
14 Wysowski D, Barash D. Adverse behavioural reactions attibuted to triazolam in the Food and Drug Administration's spontaneous reporting system. *Arch Intern Med* 1991;151:3003-8.
15 American Sleep Disorders Association. *International classification of sleep disorders diagnostics and coding manual*. Rochester, MN: ASDA, 1990.
16 Mort JR, Aparasu RR. Prescribing of psychotropics in the elderly: why is it so often inappropriate? *CNS Drugs* 2002;16:99-109.
17 Kallin K, Jensen J, Olsson LL, Nyberg L, Gustafson Y. Why the elderly fall in residential care facilities, and suggested remedies. *J Fam Pract* 2004;53:41-52.
18 Greenblatt D, Harmatz JS, Shapiro L, Engelhardt N, Gouthro TA, Shader RI. Sensitivity to triazolam in the elderly. *N Engl J Med* 1991;324:1691-8.
19 Greenblatt D, Shader RI, Harmatz JS. Implications of altered drug disposition in the elderly: studies of benzodiazepines. *J Clin Pharmacol* 1989;29:866-72.
20 Greenblatt DJ, Harmatz JS, von Moltke LL, Wright CE, Shader RI. Age and gender effects on the pharmacokinetics and pharmacodynamics of triazolam, a cytochrome P450 3A substrate. *Clin Pharmacol Ther* 2004;76:467-79.
21 Morin C, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatement efficacy. *Am J Psychiatry* 1994;151:1172-80.
22 Murtagh D, Greenwood KM. Identifying effective psychological treatments for insomnia: a meta-analysis. *J Consult Clin Psychol* 1995;63:79-89.

(Accepted 16 September 2005)

Preterm birth in twins after subfertility treatment: population based cohort study

Hans Verstraelen, Sylvie Goetgeluk, Catherine Derom, Stijn Vansteelandt, Robert Derom, Els Goetghebeur, Marleen Temmerman

Abstract

Objectives To assess gestational length and prevalence of preterm birth among medically and naturally conceived twins; to establish the role of zygosity and chorionicity in assessing gestational length in twins born after subfertility treatment.
Design Population based cohort study.
Setting Collaborative network of 19 maternity facilities in East Flanders, Belgium (East Flanders prospective twin survey).
Participants 4368 twin pairs born between 1976 and 2002, including 2915 spontaneous twin pairs, 710 twin pairs born after ovarian stimulation, and 743 twin pairs born after in vitro fertilisation or intracytoplasmic sperm injection.
Main outcome measures Gestational length and prevalence of preterm birth.
Results Compared with naturally conceived twins, twins resulting from subfertility treatment had on average a slightly decreased gestational age at birth (mean difference 4.0 days, 95% confidence interval 2.7 to 5.2), corresponding to an odds ratio of 1.6 (1.4 to 1.8) for preterm birth, albeit confined to mild preterm birth (34-36 weeks). The adjusted odds ratios of preterm birth after subfertility treatment were 1.3 (1.1 to 1.5) when controlled for birth year, maternal age, and parity and 1.6 (1.3 to 1.8) with additional control for fetal sex, caesarean section, zygosity, and chorionicity. Although an increased risk of preterm birth was therefore seen among twins resulting from subfertility treatment, the risk was largely caused by a first birth effect among subfertile couples; conversely, the risk of prematurity was substantially levelled off by the protective effect of dizygotic twinning.
Conclusions Twins resulting from subfertility treatment have an increased risk of preterm birth, but the risk is limited to mild preterm birth, primarily by virtue of dizygotic twinning.

Introduction

Efforts to increase the success rates of subfertility treatment have been accompanied by a rise in the rate of multifetal pregnancies.[1] About half of medically conceived babies in the United States and Europe are born as twins,[2 3] and almost half of all twins result from subfertility treatment.[1] Despite widespread concern about the effects of medically aided conception on perinatal outcome, few studies have investigated outcomes in twins,[4] and largely conflicting results have been reported.[5] Adverse pregnancy outcome in twins relates to the high prevalence of preterm birth and is exacerbated by monozygotic and monochorionic twinning.[6–8] Whether subfertility treatment also impinges on gestational length in twins as among singletons is unclear,[5 9] as is the extent to which type of

This is the abridged version of an article that was posted on bmj.com on 25 October 2005: http://bmj.com/cgi/doi/10.1136/bmj.38625.685706.AE

Department of Obstetrics and Gynaecology, Ghent University Hospital 1P3, De Pintelaan, B-9000 Ghent, Belgium
Hans Verstraelen *research fellow*
Marleen Temmerman *professor*
Department of Applied Mathematics and Informatics, Ghent University, B-9000 Ghent
Sylvie Goetgeluk *research fellow*
Stijn Vansteelandt *assistant professor*
Els Goetghebeur *associate professor*
Center for Human Genetics, Katholieke Universiteit Leuven, University Hospital Gasthuisberg, B-3000 Leuven, Belgium
Catherine Derom *research fellow*

continued over

BMJ 2005;331:1173–6

Association for Scientific Research in Multiple Births, B-9070 Destelbergen, Belgium
Robert Derom *professor*
Correspondence to: H Verstraelen hans.verstraelen@UGent.be

Table 1 Maternal and perinatal characteristics of the study population. Values are numbers (percentages) unless stated otherwise

Characteristic	Natural conception group (n=2915)	Ovarian stimulation group (n=710)		IVF/ICSI group (n=743)	
		Value	P value	Value	P value
Mean (SD) maternal age (years)	28.6 (4.5)	28.7 (3.7)	0.08	31.5 (3.4)	<0.001
Parity:					
0	1309 (44.9)	437 (61.5)	<0.001	509 (68.5)	<0.001
1	977 (33.5)	216 (30.4)		200 (26.9)	
≥2	629 (21.6)	57 (8.0)		34 (4.6)	
Delivery mode:					
Caesarean	752 (25.8)	242 (34.1)	<0.001	315 (42.4)	<0.001
Vaginal	2163 (74.2)	468 (65.9)		428 (57.6)	
Mean (SD) gestational age (days)	257 (20)	254 (19)	<0.001	252 (19)	<0.001
Gestational age <37 weeks	1314 (45.1)	385 (54.2)	<0.001	441 (59.4)	<0.001
Mean (SD) birth weight* (g)	2440 (570)	2390 (560)	0.02	2375 (570)	0.002
Birth weight <2500 g†	1803 (61.9)	476 (67.0)	0.009	515 (69.3)	<0.001

ICSI=intracytoplasmic sperm injection; IVF=in vitro fertilisation.
*Mean birth weight within groups calculated from mean birth weights of twin pairs constituting each group.
†Defined as at least one infant with birth weight below 2500 g.

twinning interferes with perinatal outcome after subfertility treatment.[10]

In a population based cohort we compared gestational length and preterm birth rates between naturally and medically conceived twins. We also assessed the role of zygosity and chorionicity.

Methods

Study population—Multiple births in East Flanders, Belgium, are recorded by the East Flanders prospective twin survey, through 19 maternity units.[7 8]

Data collection—Data collection has previously been described in detail.[7 8] Briefly, for every multiple birth, a defined set of obstetric and perinatal data were recorded and placentas were collected and examined within 48 hours of delivery. Zygosity and chorionicity were determined, with an accuracy of over 99%.[7 8] We estimated gestational length in days, on the basis of routine gestational dating combining last menstrual period and real time ultrasonography in early pregnancy.

Inclusion and exclusion criteria—All twins with one child weighing at least 500 g were registered. From 1 January 1976 to 31 December 2002, 4989 twin pairs were recorded. We excluded 621 twin gestations because data could not be ascertained for mode of conception (n=53), maternal age (86), parity (52), gestational length (376), zygosity (69), birth weight (19 and 23), or infant sex (2 and 3).

Definitions—We defined preterm birth as less than 37 completed weeks of gestation and low birth weight as less than 2500 g. The ovarian stimulation group included all women who conceived in vivo after any treatment regimen involving direct or indirect stimulation of ovulation. The in vitro fertilisation/intracytoplasmic sperm injection group included all women who conceived through an in vitro procedure. Both groups together comprise the subfertility group.

Outcome measures—Primary outcome measures were gestational length and rates of preterm birth according to mode of conception.

Statistical analyses—We first compared mean differences in continuous variables and differences in prevalence rates. We subsequently assessed differences in mean values and prevalence rates by fitting linear, marginal logistic, and ordinary logistic regression models. In a first set of models, we accounted for the pretreatment variables birth year, parity, and maternal age. In a second set of models, we additionally removed the mediating effects of the post-treatment variables zygosity, chorionicity, intra-twin fetal sex combination, and caesarean section

Results

Study population

The population based cohort (n=4368) comprised 2915 (66.7%) naturally conceived and 1453 (33.3%) medically conceived twin pairs, including 710 (16.3%) twin pairs born after ovarian stimulation and 743 (17.0%) twin pairs born after in vitro fertilisation or intracytoplasmic sperm injection (table 1). The dizygotic:monozygotic twinning ratio was 95.2:4.8 among medically conceived twins and 53.8:46.2 in the natural conception group (P<0.001).

Table 2 Crude and adjusted mean differences in gestational length between ovarian stimulation and IVF/ICSI groups of women, compared with natural conception group. Values are means (95% confidence intervals) unless stated otherwise

Group	Observed effect		Overall effect*		Direct effect†	
	Difference (days)	P value	Difference (days)	P value	Difference (days)	P value
Natural conception (n=2915)	Reference	–	Reference	–	Reference	–
Ovarian stimulation (n=710)	3.2 (1.6 to 4.9)	<0.001	1.9 (0.3 to 3.6)	0.02	3.4 (1.7 to 5.2)	<0.001
IVF/ICSI (n=743)	4.6 (3.0 to 6.2)	<0.001	2.3 (0.5 to 4.1)	0.01	3.9 (2.0 to 5.8)	<0.001
Subfertility treatment‡ (n=1453)	4.0 (2.7 to 5.2)	<0.001	2.1 (0.7 to 3.5)	0.003	3.6 (2.2 to 5.1)	<0.001

ICSI=intracytoplasmic sperm injection; IVF=in vitro fertilisation.
*Multivariable analysis accounting for birth year, maternal age, and parity (confounders).
†Multivariable analysis accounting for birth year, maternal age, and parity (confounders) and for infant sex, caesarean delivery, zygosity, and chorionicity (mediating variables).
‡Comprises ovarian stimulation and IVF/ICSI groups.

Table 3 Crude and adjusted odds ratios (95% confidence intervals) of preterm birth in ovarian stimulation and IVF/ICSI groups of women, compared with natural conception group

	Observed effect		Overall effect*		Direct effect†	
Group	Odds ratio	P value	Odds ratio	P value	Odds ratio	P value
Natural conception (n=2915)	Reference	–	Reference	–	Reference	–
Ovarian stimulation (n=710)	1.44 (1.22 to 1.70)	<0.001	1.26 (1.07 to 1.50)	0.007	1.42 (1.18 to 1.70)	<0.001
IVF/ICSI (n=743)	1.78 (1.51 to 2.10)	<0.001	1.38 (1.15 to 1.66)	<0.001	1.58 (1.30 to 1.92)	<0.001
Subfertility treatment‡ (n=1453)	1.61 (1.41 to 1.82)	<0.001	1.32 (1.14 to 1.51)	<0.001	1.49 (1.27 to 1.73)	<0.001

ICSI=intracytoplasmic sperm injection; IVF=in vitro fertilisation.
*Multivariable analysis accounting for birth year, maternal age, and parity (confounders).
†Multivariable analysis accounting for birth year, maternal age, and parity (confounders) and for infant sex, caesarean delivery, zygosity, and chorionicity (mediating variables).
‡Comprises ovarian stimulation and IVF/ICSI groups.

Differences in gestational length and risk of preterm birth

Subfertility treatment was associated with a small decrease in gestational age at birth compared with the natural conception group (tables 1 and 2). This difference translated to an odds ratio of 1.6 (95% confidence interval 1.4 to 1.8) for preterm birth (table 3), confined to mild preterm birth (≥34 weeks). Medically conceived twins were more likely to be preterm delivered by caesarean section (odds ratio 1.5, 1.2 to 1.9) but were also at higher risk of spontaneous preterm birth (odds ratio 1.6, 1.4 to 1.8). Medically conceived twins had a slightly lower average birth weight (table 1).

Adjusted differences in gestational length and risk of preterm birth

We estimated the "overall" effect of subfertility treatment by adjusting the outcomes for birth year, maternal age, and parity. Differences in gestational length (table 2) and preterm birth rate (table 3) were attenuated when we accounted for confounding; lower parity among women who conceived medically was the strongest confounder. The observed effects were, however, not entirely explained by these confounding effects.

To assess the "direct" effect of subfertility treatment, we additionally accounted for zygosity, chorionicity, fetal sex, and delivery mode, which act on the pathway from conception to birth as intermediate variables to the outcomes assessed. The increased effect size of the direct effect on gestational length (table 2) and preterm birth (table 3) over and above the overall effect was mainly attributable to the effect of zygosity. Chorionicity had a marginal effect on gestational length beyond zygosity. Dizygotic twinning pertaining to iatrogenic pregnancy therefore proves a strong and advantageous mediator of gestational length (table 3).

Discussion

Twins resulting from in vivo conception after ovarian stimulation or from in vitro conception with assisted reproduction technologies have a slightly decreased gestational age at birth and incur an increased risk of mild preterm birth compared with naturally conceived twins. This is largely explained by a first birth effect among the subfertility groups of women; conversely, gestational length substantially benefits from predominantly dizygotic twinning after subfertility treatment.

Limitations of the study

The main shortcoming of this study is the lack of data on potential confounding by socioeconomic status. We cannot be sure that women of higher social classes were not over-represented in the subfertility group. Overall, inferences in this study rely on a defined set of confounders. Our findings must be interpreted with caution, as we cannot be certain that residual confounders have not been accounted for. Furthermore, no inferences can be made on subfertility treatment as such, because we compared subfertile couples with naturally conceiving couples, and the former were exposed to both subfertility and treatment for subfertility. Similarly, as the ovarian stimulation and in vitro fertilisation/intracytoplasmic sperm injection groups of women probably differed in many respects, no comparisons can be made between these in terms of subfertility treatment alone.

Strengths of the study

This is the first population based twin study in which subfertility treatment per se, rather than assisted reproductive technologies alone, made up the exposure variable. No previous study properly accounted for the role of zygosity and chorionicity in assessing perinatal outcomes after subfertility treatment through systematic determination of twinning type.

Subfertility treatment as a risk factor for preterm birth

The fact that subfertility has been consistently associated with adverse perinatal outcome in singleton gestation, but less so in twin gestations,[5] challenges the prevailing paradigm that subfertile patients per se incur an increased obstetric risk.[11] As a putative explanation, most medically aided pregnancies result from multiple conception, so those that continue as twin pregnancies may start off with a relative advantage.[5 12] Although this is plausible, it is probably as true for natural twin pregnancies, considering that only one in eight fetuses originating as a twin goes on to be born as a twin.[13]

It has further been postulated that predominantly dizygotic or dichorionic twinning also gives medically conceived twins an advantage. Dizygotic twinning did prove an important protective feature pertaining to ovarian stimulation and assisted reproduction in our study.

Magnitude of the risk

Among singletons resulting from assisted reproduction, two recent meta-analyses showed a 5.3-6.2% excess rate of preterm birth (from 6.1% to 11.4%[5] and from 5.3% to 11.5%[9]), corresponding to an odds ratio of 2.0. The odds ratios in our study were lower, but this should not be misconstrued,[14] considering the 10-fold higher prevalence of preterm birth among twins compared with singletons. We observed an excess preterm birth rate of 11.7%, twice the excess rate reported in singletons. The effects on mean gestational length, and therefore on the degree or severity of prematurity, are

What is already known on this topic

Half of all children resulting from subfertility treatment are born as twins; most of these are dizygotic

Unlike singletons, twins resulting from subfertility treatment are not deemed to have worse perinatal outcome than their naturally conceived counterparts

What this study adds

Twins conceived through artificial induction of ovulation with or without subsequent in vitro fertilisation had on average a slightly decreased gestational age at birth

This difference corresponded to a 60% increased odds of preterm birth after subfertility treatment compared with natural conception

The risk was confined to mild preterm birth at 34-36 weeks, primarily by virtue of dizygotic twinning with subfertility treatment

less pronounced than in singletons,[5] by virtue of dizygotic twinning after subfertility treatment.

Comparison with other studies

We identified no similar population based studies in which gestational length in twins was compared according to fertility status or mode of conception. Previous studies may be affected by misclassification bias through allocating women who conceived after ovarian stimulation to the natural conception group.[6]

At least five previous studies attempted to partially control for zygosity by confining the analyses to twins of unlike sex,[6 12 15–17] as an incomplete proxy for zygosity, which may explain why the effect of zygosity was not apparent.[5] Recognition of zygosity and chorionicity is a labour intensive procedure, so data on type of twinning are usually not available from birth or twin registries.

Conclusions and recommendations

Subfertility treatment is associated with a certain degree of prematurity over and above the intrinsic preterm birth risk of multiplicity. This is important to the extent that an ever increasing number of babies result from subfertility treatment, half of these being twins, while on the whole twins contribute disproportionately to the prematurity related disease burden. It is equally important to recognise that gestational length after subfertility treatment is largely determined by maternal characteristics, whereas primarily dizygotic twinning pertaining to subfertility treatment seems to be a strong and clinically advantageous feature of medically conceived twins.

Apposite consideration of altered zygosity distributions after subfertility treatment, and ascertainment of mode of conception, are imperative to future research on perinatal outcome and infant health in twins. Although efforts are being made to counteract multifetal pregnancy rates through elective single embryo transfer, the "multiple birth epidemic" may continue as a result of the wide use of ovulation inducing agents.

We thank all East Flemish maternity facilities and gynaecologists for their longstanding and continued support for the survey. We also thank midwives Lut De Zeure and Ingeborg Berckmoes for their excellent fieldwork and technical assistance.

Contributors: See bmj.com

Funding: From its inception, the East Flanders prospective twin survey has been partly supported by grants from the Fund of Scientific Research, Flanders, and by the Association for Scientific Research in Multiple Births (vzw Twins). This study was supported through grants from the Ghent University Research Fund (HV) and the Institute for the Promotion of Innovation through Science and Technology in Flanders (IWT-Vlaanderen) (SG). As the main funding sources, the Ghent University Research Fund and the Institute for the Promotion of Innovation through Science and Technology were not involved in designing the study, the conduct of the study, drafting the manuscript, or the decision to publish. SV is a postdoctoral research fellow of the Fund for Scientific Research, Flanders.

EG is also adjunct associate professor, Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115, USA. Competing interests: None declared.

Ethical approval: Ghent University hospital ethical board approved the study protocol.

1 Blondel B, Kaminski M. Trends in the occurrence, determinants, and consequences of multiple births. *Semin Perinatol* 2002;26:239-49.
2 Wright VC, Schieve LA, Reynolds MA, Jeng G. Assisted reproductive technology surveillance—United States, 2000. *MMWR Surveil* 2003;52:1-16.
3 Nyboe Andersen A, Gianaroli L, Nygren KG, European IVF-monitoring programme, European Society of Human Reproduction and Embryology. Assisted reproductive technology in Europe, 2000: results generated from European registers by ESHRE. *Hum Reprod* 2004;19:490-503.
4 Blondel B, Macfarlane A. Rising multiple maternity rates and medical management of subfertility: better information is needed. *Eur J Public Health* 2003;13:83-6.
5 Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ* 2004;328:261.
6 Pinborg A, Loft A, Rasmussen S, Schmidt L, Langhoff-Roos J, Greisen G, et al. Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10,362 non-IVF/ICSI twins born between 1995 and 2000. *Hum Reprod* 2004;19:435-41.
7 Derom C, Derom R. The East Flanders prospective twin survey. In: Blickstein I, Keith LG, eds. *Multiple pregnancy: epidemiology, gestation and perinatal outcome*. 2nd ed. Oxon: Taylor and Francis, 2005:39-47.
8 Loos R, Derom C, Vlietinck R, Derom R. The East Flanders prospective twin survey (Belgium): a population-based register. *Twin Res* 1998;1:167-75.
9 Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. *Obstet Gynecol* 2004;103:551-63.
10 Machin GA. Why is it important to diagnose chorionicity and how do we do it? *Best Pract Res Clin Obstet Gynaecol* 2004;18:515-30.
11 Basso O, Baird DD. Infertility and preterm delivery, birth weight, and caesarean section: a study within the Danish national birth cohort. *Hum Reprod* 2003;18:2478-84.
12 Dhont M, De Sutter P, Ruyssinck G, Martens G, Bekaert A. Perinatal outcome of pregnancies after assisted reproduction: a case-control study. *Am J Obstet Gynecol* 1999;181:688-95.
13 Hall JG. Twinning. *Lancet* 2003;362:735-43.
14 Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ* 1998;316:989-91.
15 Moise J, Laor A, Armon Y, Gur I, Gale R. The outcome of twin pregnancies after IVF. *Hum Reprod* 1998;13:1702-5.
16 Koudstaal J, Bruinse HW, Helmerhorst FM, Vermeiden JP, Willemsen WN, Visser GH. Obstetric outcome of twin pregnancies after in-vitro fertilization: a matched control study in four Dutch university hospitals. *Hum Reprod* 2000;15:935-40.
17 Lambalk CB, van Hooff M. Natural versus induced twinning and pregnancy outcome: a Dutch nationwide survey of primiparous dizygotic twin deliveries. *Fertil Steril* 2001;75:731-6.

(Accepted 16 September 2005)

doi 10.1136/bmj.38625.685706.AE

Endpiece

Qualities of a surgeon

A surgeon should be youthful or at any rate nearer youth than age; with a strong and steady hand that never trembles, and ready to use the left hand as well as the right; with vision sharp and clear, and spirit undaunted; filled with pity, so that he wishes to cure the patient, yet is not moved by his cries, to go too fast, or cut less than is necessary; but he does everything just as if the cries of pain cause him no emotion.

Celsius, *De Medecina Book VII*

Submitted by S N Anjum, P Quinn, and R Anwar
Department of Orthopaedics, Maidstone General Hospital, Maidstone, Kent