Review of unexplained infertility and obstetric outcome: a 10 year review

Zabeena Pandian[1], Siladitya Bhattacharya and Allan Templeton

Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen AB25 2ZD, UK

[1]To whom correspondence should be addressed. E-mail: z.pandian@abdn.ac.uk

BACKGROUND: Increased maternal and fetal risks have been reported in pregnancies following unexplained infertility. Our aims were to examine the obstetric and perinatal outcome of singleton pregnancies in couples with unexplained infertility and explore the impact of fertility treatment. METHODS: Women with unexplained infertility were identified from the Aberdeen Fertility Clinic Database. Their unit numbers were matched against the Aberdeen Maternity and Neonatal Databank (AMND) in order to extract obstetric records of those women with subsequent pregnancy outcomes. The general obstetric population served as a control group. RESULTS: Women with unexplained infertility were older [30.8 versus 27.9 years, 95% confidence interval (CI) for difference = +2.4 to +3.4] and more likely to be primiparous (59 versus 40%, 95% CI = +1.3 to +1.9). After adjusting for age and parity they had a higher incidence of pre-eclampsia, abruptio placentae, preterm labour, emergency Caesarean section and induction of labour in comparison with the general population ($P < 0.05$). Perinatal outcome did not differ between women with unexplained infertility and those of the general population. The multiple pregnancy rate was 5.4% higher following fertility treatment than in women who conceived spontaneously (95% CI = +2.8 to +9.7). CONCLUSIONS: Women with unexplained infertility are at higher risk of obstetric complications which persist even after adjusting for age, parity and fertility treatment. The reasons are however unclear and merit further study.

Key words: obstetric outcome/perinatal outcome/treatment-independent/treatment-related/unexplained infertility

Introduction

Pregnancies in women with infertility have been linked with increased maternal and perinatal risks (Ghazi *et al.*, 1991; Rizk *et al.*, 1991; Tan *et al.*, 1992). Most complications have been attributed to the higher number of multiple pregnancies after fertility treatment but even singleton pregnancies have been shown to be associated with increased rates of vaginal bleeding, placenta praevia, pregnancy induced hypertension and Caesarean section (Tan *et al.*, 1992; McFaul *et al.*, 1993). Higher perinatal risks, including prematurity, intrauterine growth retardation and low birth weight have also been highlighted in these pregnancies (Ghazi *et al.*, 1991; Sundstrom *et al.*, 1997) although, in the absence of multiple pregnancies, the cause for this phenomenon has yet to be identified. It is unclear from previous studies (Wang *et al.*, 1994; Isaksson and Tiitinen, 1998) if these effects are associated with patient characteristics (older age and primiparity) or some unknown factor intrinsic to these couples. In addition, the relative contribution of fertility treatment itself remains unexplored.

A quarter of all infertile couples have unexplained infertility (Templeton and Penney, 1982). In comparison with other groups, these couples experience a relatively high spontaneous pregnancy rate (Templeton and Penney, 1982; Collins *et al.*,

1995), but also face the prospect of treatment, which in the absence of a diagnosed cause is essentially empirical. These are important considerations which should be taken into account when deciding the timing and choice of treatment, especially if treatment has the potential to increase maternal and fetal risks.

We aimed to assess the obstetric risks associated with unexplained infertility and explore the factors responsible for them by comparing firstly, the outcome of pregnancy in couples with unexplained infertility with that in the general population and secondly, treatment-related and treatment-independent pregnancies. As many of these risks are associated with multiple pregnancies, these were excluded from our analysis. The presence of two large local databases [The Aberdeen Maternity and Neonatal Databank (AMND) and the Aberdeen Fertility Clinic database] and the presence of a relatively stable population in the north-east of Scotland allowed us to perform these comparisons. The AMND contains information on all obstetric and fertility related gynaecological events in women in a defined geographical area (Aberdeen City District) with a stable catchment population since 1951 (Samphier and Thompson, 1981). Stringent and consistent criteria, which are essential both for studies of secular change and for intergenerational studies, have been used for the coding

of gestational length, birth weight, pregnancy complications and the classification of perinatal events. Since 1989 the Aberdeen Fertility Clinic database has collected information prospectively related to all couples referred to the Fertility Clinic and contains detailed case records of more than 4000 couples. Record linkage allows easy identification of complete reproductive histories of individuals as well as families.

Materials and methods

Couples resident in Aberdeen with unexplained infertility of more than 12 months duration were identified from the Fertility Clinic database. Infertility history and treatment details of couples seen between March 1989 and March 1999 were also derived from the database. The following criteria were used to make a diagnosis of unexplained infertility: mid-luteal serum progesterone concentration >20 nmol/l, bilateral tubal patency demonstrated by laparoscopy or hysterosalpingogram and normal semen parameters (World Health Organization, 1999). Follow-up of the couples was for a minimum of 12 months.

Obstetric records of the women with unexplained infertility were identified from the AMND by using name and unit number. Data related to maternal and perinatal complications were obtained, and the results were then compared with the figures for the local obstetric population during the same period of time. The outcomes of spontaneous and treatment-related pregnancies were also compared. Only the first delivery that occurred after the onset of investigation was studied.

Multiple pregnancies were excluded from the analysis because they carry a higher risk of obstetric and perinatal complications in comparison with singleton pregnancies. As birth weight is not normally distributed at each week of gestation, birth weights were assessed using standardized birth weight score (SBW) which adjusts for parity, gestation and sex of the newborn (Campbell *et al*., 1993).

Statistics

Statistical analysis was carried out using the statistical package SPSS for windows (Statistical Package for Social Sciences). Student's *t*-test, the Mann–Whitney *U*-test, Fisher's exact test and χ^2 test were used where appropriate. Confidence intervals were calculated using the CIA programme (Wilson's method).

Logistic regression was used to calculate unadjusted and adjusted odds ratios where indicated.

Results

A total of 1049 couples with unexplained infertility was initially identified from the Fertility Clinic database; 172

couples were subsequently excluded from analysis due to insufficient data. Of the remaining 877 couples, 498 (57%) had a pregnancy outcome and were analysed in detail. The relevant infertility treatments and the percentage of women requiring them were: administration of clomiphene citrate (39%), ovulation induction and intrauterine insemination (11%) and IVF (50%). Characteristics of the women with unexplained infertility are shown in Table I.

The general population which comprised the comparison group consisted of 32 969 singleton deliveries during the same period of time (1989–1999). In comparison with the general obstetric population, women with unexplained infertility who delivered were significantly older. The mean (SD) age in the two groups were 30.8 (4.5) versus 27.9 (5.3) years, 95% confidence interval (CI) for difference = +2.2 to +3.2. Infertile women were also more likely to be primiparous (59 versus 40%, 95% CI for difference = +1.3 to +1.9).

The outcome of pregnancies in women with unexplained infertility is shown in Figure 1. The multiple pregnancy rate was 5.4% higher in the treatment group compared with the spontaneous pregnancy group (95% CI for difference = +2.8 to +9.7).

Obstetric complications

Table II shows the incidence of obstetric complications among singleton live births in couples with unexplained infertility. When compared with the general population, the incidence of pre-eclampsia, placental abruption and preterm labour between 24 and 37 completed weeks of gestation was significantly higher in women with unexplained infertility ($P < 0.05$). Obstetric interventions including Caesarean sections and induction of labour ($P < 0.05$) were also more common. Table III demonstrates that these differences were significant even after adjusting for differences in age and parity between women with unexplained infertility and the general population. There were no differences in obstetric interventions or complications between the treatment-independent and treatment-related pregnancies.

Perinatal outcome

Table IV summarizes the perinatal outcome of singleton births. When compared with the general population the mean [SD] duration of pregnancy and the apgar scores at 1 min and 5

Table I. Characteristics of women with unexplained infertility who delivered singletons babies. Values are given as *n* (%) or mean (SD) unless otherwise stated

	Treatment-independent *n* = 222	Treatment-related *n* = 162	Difference (95% CI)
Maternal age (years)	30.6 (4.1)	30.9 (4.7)	0.3 (−1.2 to +5.8)
Maternal age ≤35 years	183 (82)	143 (88)	6 (−1.3 to +0.1)
Maternal age >35 years	39 (18)	19 (12)	6 (−0.2 to +1.3)
Duration of infertility (years)[a]	3.2 (5.5)	3.78 (2.1)	0.58 (−1.34 to +0.18)
Duration of follow-up (years)	6.2 (2.5)	6.2 (2.5)	0 (−0.44 to +0.44)
Primary infertility	131 (59)	97 (60)	1 (−1.1 to +0.9)
Secondary infertility	91 (41)	65 (40)	1 (−0.9 to +1.1)

[a]Number of years of infertility at presentation plus the number of years from presentation up to conception.
CI = confidence interval.

min were lower in the infants of these couples but still within the normal range. There were no significant differences in the perinatal outcome between the treatment-independent and treatment-related singleton births.

Discussion

Our results suggest that even in the absence of multiple pregnancy, women with unexplained infertility face an increased likelihood of obstetric complications which are independent of age, parity and fertility treatment. However, the perinatal outcome appears to be unchanged.

This is the largest descriptive study focusing on couples with unexplained infertility. Collection of data from both the Fertility Clinic database and the AMND was done prospectively, thus reducing recall bias. Standardized birthweight score (SBW) was preferred to crude birthweight in determining differences in birth weights of infants of the couples in the study.
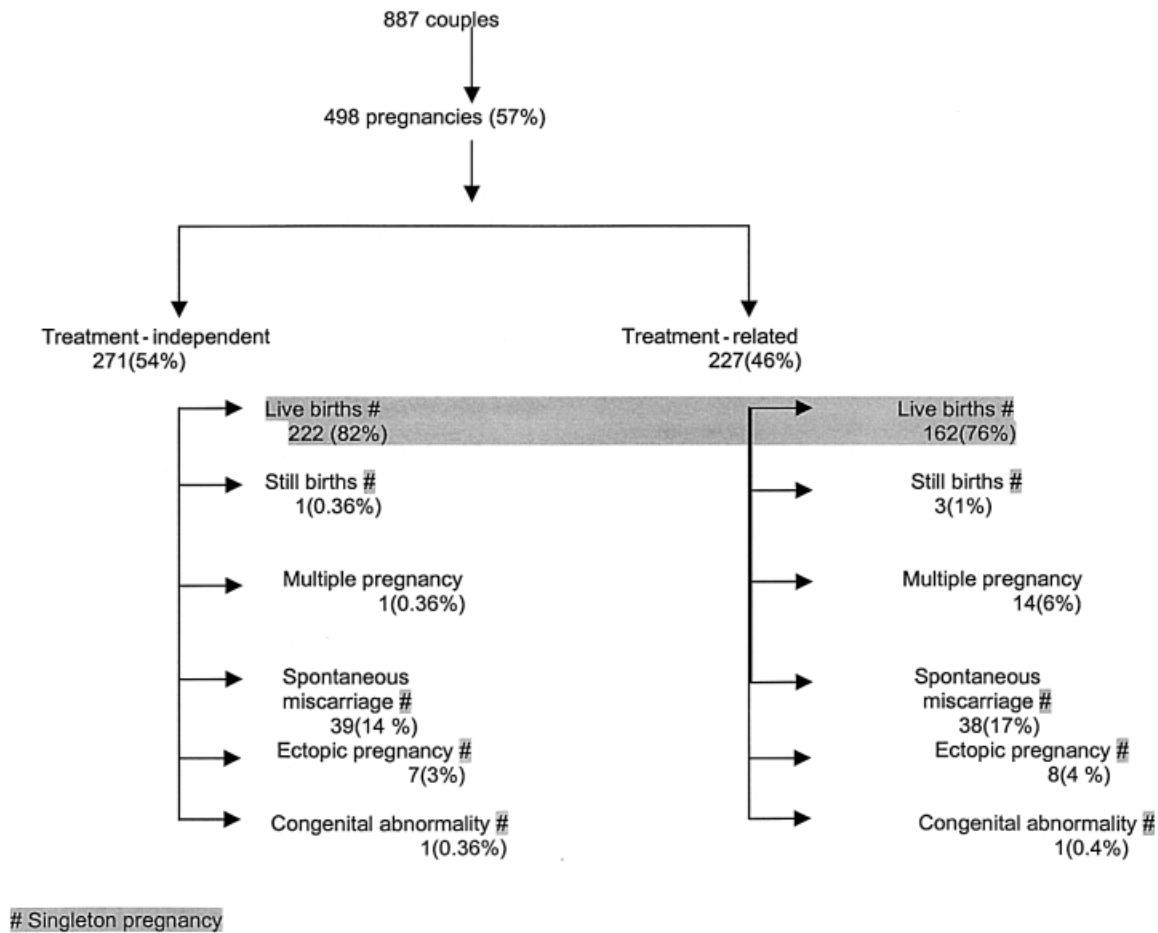
Figure 1. Outcome of spontaneous and treatment-related pregnancies.

Table II. Obstetric complications in women with unexplained infertility (singletons only). Values are given as *n* (%) unless otherwise stated

	Couples with unexplained infertility *n* = 369	Total population	Difference (95% CI) *n* = 32 969	Treatment-independent *n* = 222	Treatment-related *n* = 162	Difference (95% CI)
Pre-eclampsia	18 (5)	659 (2)	3 (+1.1 to +5.6)	10 (4)	8 (5)	1 (−0.2 to +3.6)
Eclampsia	1 (0.3)	33 (0.1)	0.2 (−0.1 to +1.4)	1 (0.4)	0 (0)	0.4 (−2.1 to +2.5)
Abruption (APH)	7 (2)	230 (0.7)	1.3 (+0.2 to +3.2)	3 (1)	4 (2)	1 (−5.5 to +1.7)
Placenta praevia	3 (0.8)	132 (0.4)	0.4 (−0.1 to +2)	2 (0.9)	1 (0.6)	0.3 (−2.9 to +2.6)
Gestation at delivery						
24–37 weeks	41 (11)	1912 (6)	5 (+2.5 to +8.9)	23 (10)	18 (12)	2 (−8.9 to +4.7)
≥37 weeks	328 (89)	30 990 (94)	5 (−8.7 to −1.9)	198 (90)	130 (88)	2 (−4.7 to +8.9)
Induced labour	105 (28)	7253 (22)	6 (+2.1 to +11.3)	63 (28)	42 (28)	0 (−9.4 to +9.3)
Elective Caesarean sections	23 (6)	1846 (5)	1 (−1.4 to +3.6)	14 (6)	9 (6)	0 (−5.4 to +5.2)
Emergency Caesarean sections	75 (20)	3066 (9)	11 (+7.2 to +15.4)	42 (19)	33 (22)	3 (−12 to +4.9)

Some difficulties were encountered during this study. In comparison with the general population, women with unexplained infertility are usually older and are less likely to have had previous deliveries. Multiple births are common and a significant proportion of women would have been exposed to assisted reproductive techniques. Under these conditions, identification of an appropriate matched control can be difficult (McFaul *et al.*, 1993). We decided to use women who conceived spontaneously and delivered between 1989 and 1999 in Aberdeen as a comparison group and adjusted for differences in age and parity. Only data relating to singletons were analysed in order to avoid the possible confounding effects of multiple pregnancies.

We also made the assumption that the details of all women who were resident in Aberdeen and had a pregnancy outcome during the period of the study would be registered with the AMND. Although there is a possibility that a small number of women could have delivered elsewhere, the relative stability of the Aberdeen population which has an out-migration rate (including deaths) of about 3% (Hall *et al.*, 1989), ensures that those delivering elsewhere constitute a small minority.

The literature surrounding obstetric outcome in couples with unexplained infertility is very limited. Most studies involve relatively small numbers of patients with limited follow-up (Sundstrom *et al.*, 1997; Isaksson and Tiitinen, 1998). The results of our study agree with some previous reports (Saunders *et al.*, 1988; Reubinoff *et al.*, 1997; Isaksson and Tiitinen,

1998) which suggest that infertility treatment *per se* is not associated with a higher incidence of pre eclampsia, abruption and preterm deliveries. In contrast to previous reports (Tuck *et al.*, 1988; Li *et al.*, 1991), our study fails to confirm a link between these complications and advanced maternal age.

In comparison with the general population, there seemed to be a lower threshold for obstetric interventions including induction of labour and Caesarean sections in couples with unexplained infertility. Contrary to findings from previous studies (Reubinoff *et al.*, 1997), fertility treatment did not seem to influence the rate of Caesarean sections. Overall, the lower threshold for obstetric interventions in these couples could be partly attributed to the anxiety around these pregnancies and the influence of a history of infertility on the clinician's decision making.

The results of our study indicate no increase in perinatal risks in couples with unexplained infertility. Adverse perinatal outcomes including stillbirth, low birth weight, neonatal unit admissions, and early and late neonatal deaths in women undergoing assisted reproduction treatment have been reported by various authors (Rizk *et al.*, 1991; McFaul *et al.*, 1993). The comparable birth weights in the treatment-independent and treatment-related groups observed in our study concur with results of some studies (Frydman *et al.*, 1986; Hill *et al.*, 1990; Reubinoff *et al.*, 1997) but not with others (Rizk *et al.*, 1991; McFaul *et al.*, 1993; Olivennes *et al.*, 1997). The disparity of the results in the literature may be due to differences in statistical power, study design, choice of controls and the possible confounding effects of premature babies. For many of the rarer events of interest, especially perinatal mortality, a much larger number of patients is required to provide the statistical power necessary to draw any firm conclusions. In comparison with other published reports (Beral and Doyle, 1990; Bergh *et al.*, 1999; SART registry, 1999) the group of patients who underwent assisted reproduction treatment in our study was small.

Women with a history of unexplained infertility are perhaps more closely monitored than others and consequently have a

Table III. Risk of obstetric complications in women with unexplained infertility (singletons only)

	Unadjusted odds ratio (95% CI)	Odds ratio adjusted for age and parity (95% CI)
Placental abruption	2.93 (1.4–5.9)	3.05 (1.4–6.2)
Pre-eclampsia	6.16 (3.7–10.1)	5.61 (3.3–9.3)
Caesarean section	1.95 (1.5–2.4)	1.46 (1.1–1.8)
Induction of labour	1.31 (1.0–1.6)	1.24 (1.0–1.5)

Table IV. Perinatal outcome in couples with unexplained infertility (singleton births). Values are given as *n* (%) or mean (SD) unless otherwise stated

	All couples with unexplained infertility *n* = 384	Total population *n* = 32 969	Difference (95% CI)	Treatment-independent *n* = 222	Treatment-related *n* = 162	Difference (95%CI)
Gestation (weeks)						
Mean (SD)	38.93 (2.67)	39.40 (1.90)	0.47 (−0.66 to −0.27)	39.05 (2.49)	38.77 (2.88)	0.28 (−0.26 to +0.82)
Sex						
Male	225 (58)	16 814 (51)	7 (+2.1 to +11.9)	132 (59)	93 (57)	2 (−6.6 to +13.2)
Female	159 (41)	16 154 (49)	8 (−12.4 to −2.6)	90 (40)	69 (43)	3 (−12.0 to +7.8)
Apgar score at 1 min						
Mean (SD)	7.74 (1.98)	8.07 (1.56)	0.33 (−0.48 to −0.17)	7.83 (1.85)	7.62 (2.14)	0.21 (−0.19 to +0.61)
Apgar score at 5min						
Mean (SD)	8.70 (1.56)	8.95 (0.69)	0.25 (−0.32 to −0.17)	8.78 (1.39)	8.60 (1.76)	0.18 (−0.13 to +0.49)
Standardized birth weight score	0.10 (1.03)	0.023 (0.99)	0.08 (−3.3 to +16.7)	0.05 (1.06)	0.14 (1.02)	0.09 (−30.2 to +12.2)
Admissions to neonatal unit	38 (10)	2637 (8)	2 (−0.7 to +5.3)	23 (10)	15 (9)	1 (−5.3 to +7.0)
First day neonatal death	1 (0.3)	45 (0.1)	0.2 (−0.1 to +1.4)	0 (0)	1 (0.6)	0.6 (−3.4 to +1.2)
First week neonatal death (excluding 1st day death)	1 (0.3)	28 (0.1)	0.2 (−0.1 to +1.4)	0 (0)	1 (0.6)	0.6 (−3.4 to +1.2)

higher pick-up rate of any potential problems. This may lead to an increased diagnosis of obstetric complications and a greater chance of surgical intervention. Traditionally, a higher complication rate in these women has been ascribed to increased maternal age and a higher proportion of multiple pregnancies. Our study shows that these risks persist even after adjusting for these factors. Apart from increasing the chance of multiple pregnancy, fertility treatment *per se* does not increase either the complication rate or the rate of intervention in these women. Although a lower threshold for intervention cannot be ruled out, women with unexplained infertility may be a genuine high risk group who would benefit from better counselling and additional care. More work is needed to explore the link between obstetric complications and unexplained infertility.

References

Beral, V. and Doyle, P. (1990) MRC working party on children conceived by *in vitro* fertilisation; births in Great Britain resulting from assisted conception 1978–1987. *Br. Med. J.*, **300**, 1229–1233.

Bergh, T., Ericson, A., Hillensjo, T. *et al.* (1999) Deliveries and children born after *in vitro* fertilisation in Sweden 1982–95; a retrospective cohort study. *Lancet*, **354**, 1579–1585.

Campbell, D., Hall, M., Lemon, J. *et al.* (1993) Clinical birth weight standards for a total population in the 1980s. *Br. J. Obstet. Gynaecol.*, **100**, 436–445.

Collins, J.A., Elizabeth, A.B. and Willan, A.R. (1995) The prognosis for live birth among untreated infertile couples. *Fertil. Steril.*, **64**, 22–28.

Frydman, R., Belaisch-Allart, J., Fries, N. *et al.* (1986) An obstetric assessment of the first 100 births from the invitro fertilisation program at Clamart, France. *Am. J. Obstet. Gynecol.*, **154**, 550–555.

Ghazi, H.A., Spielberger, C. and Kallen, B. (1991) Delivery outcome after infertility – a registry study. *Fertil. Steril.*, **55**, 726–732.

Hall, M.H., Campbell, D.M., Fraser, C. *et al.* (1989) Mode of delivery and future fertility. *Br. J. Obstet. Gynaecol.*, **96**, 1297–1303.

Hill, G.A., Bryan, S., Herbert, C.M. III *et al.* (1990) Complications of pregnancy in infertile couples: routine versus assisted reproduction. *Obstet. Gynaecol.*, **75**, 790–794.

Isaksson, R. and Tiitinen, A. (1998) Obstetric outcome in patients with unexplained infertility: comparison of treatment-related and spontaneous pregnancies. *Acta Obstet. Gynecol. Scand.*, **77**, 849–853.

Li, T.C., MacLeod, I., Singhal, V. *et al.* (1991) The obstetric and neonatal outcome of pregnancies in women with previous history of infertility, a prospective study. *Br. J. Obstet. Gynaecol.*, **98**, 1087–1092.

McFaul, P.B., Patel, N. and Mills, J. (1993) An audit of the obstetric outcome of 148 consecutive pregnancies from assisted conception. Implications for neonatal services. *Br. J. Obstet. Gynaecol.*, **100**, 820–825.

Olivennes, F., Kerbrat, V., Rufat, P. *et al.* (1997) Follow-up of a cohort of 422 children aged 6–13 years conceived by *in vitro* fertilisation. *Fertil. Steril.*, **67**, 284–289.

Reubinoff, B.E., Samueloff, A., Ben-Haim, M. *et al.* (1997) Is the obstetric outcome of *in vitro* fertilized singleton gestations different from natural ones? A controlled study. *Fertil. Steril.*, **67**, 1077–1083.

Rizk, B., Doyle, P., Tan, S.L. *et al.* (1991) Perinatal outcome and congenital malformations in IVF babies from Bourn Hallam group. *Hum. Reprod.*, **6**, 1259–1264.

Samphier, M. and Thompson, B. (1981) The Aberdeen maternity and neonatal databank. In Mednick, S.A. and Baert, A.E. (eds) *Prospective longitudinal research*. Oxford University Press, Oxford, pp. 61–65.

SART Registry (1999) Assisted reproductive technology in the United States: 1996 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry. *Fertil. Steril.*, **71**, 798–807.

Saunders, D.M., Mathew, M. and Lancaster, P.A.L. (1988) The Australian Register: current research and future role. A preliminary report. *Ann. N. Y. Acad. Sci.*, **541**, 7–21.

Sundstrom, I., Ildgruben, A. and Hogberg, U. (1997) Treatment related and treatment independent deliveries among infertile couples, a long term follow up. *Acta Obstet. Gynecol. Scand.*, **76**, 238–243.

Tan, S.L., Doyle, P., Campbell, S. *et al.* (1992) Obstetric outcome of *in vitro* fertilisation pregnancies compared with normally conceived pregnancies. *Am. J. Obstet. Gynecol.*, **167**, 778–784.

Templeton, A.A. and Penney, G.C. (1982) The incidence, characteristics and prognosis of patients whose infertility is unexplained. *Fertil. Steril.*, **37**, 175–182.

Tuck, S.M., Yudkin, P.L. and Turnbull, A.C. (1988). Pregnancy outcome in elderly primigravida with and without a history of infertility. *Br. J. Obstet. Gynaecol.*, **95**, 230–237.

Wang, X.J., Clark, A.M., Kirby, C.A. *et al.* (1994) The obstetric outcome of singleton pregnancies following in-vitro fertilization/gamete intra-Fallopian transfer. *Hum. Reprod.*, **9**, 141–146.

World Health Organization (1999) *Laboratory manual for the examination of human semen and sperm–cervical mucus interaction*. Cambridge University Press, Cambridge, pp. 60–61.