of induced abortions (25·9%) and a lower proportion of deliveries (66·8%) than did the PACA region: 23·5% and 68·7%, respectively. However, no significant differences were seen in the proportion of spontaneous abortion (6·3% *vs* 6·8%) and ectopic pregnancy (1%). Age adjustment (direct method) did not modify our findings.

Combining the results of the two regions, the rate of spontaneous abortion (defined as the proportion of spontaneous abortions among all the pregnancies) was 6·5% and increased with age (5·1% in women aged 15 to 19 years to 15·7% in women aged 40 to 44 years). The incidence of ectopic pregnancy was 1% and varied from 0·6% in the youngest age groups (15 to 19 years and 20 to 24 years) to 1·8% (35 to 39 years) and 1·3% (40 to 44 years).

Since our survey included almost all medical centres and thus nearly all women at the end of pregnancy, the results provide a good estimate of the number of pregnancy outcomes. However, women who had a very early spontaneous abortion were not included since they would not usually be admitted to hospital. The comparison with studies published since 1980 is difficult due to different denominators. However, the rate of spontaneous abortion (6·5%) in our study is lower than that (10·2%) found in 1983 in the Finnish nationwide database (Lindbohm & Hemminki 1988), but ectopic pregnancies were not included in the denominator. The incidence rate of ectopic pregnancy (1%) in our study is close to that reported in 1983 in the United States (14/1000 reported pregnancies) (Centers for Disease Control 1986) but spontaneous abortions were not included.

The major strength of our study was to record all pregnancy outcomes over defined periods in large geographical sites in order to estimate better the true denominator. Repetition of the study with the same methodology will provide trends in the rates of pregnancy outcomes. Furthermore, the development of similar studies planned in Europe will allow valid between-country comparisons in rates of pregnancy outcomes.

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Maternal alpha-fetoprotein levels in multiple pregnancies

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Subjects and methods

Maternal serum alpha-fetoprotein (MSAFP) was measured in 12 multifetal pregnancies before and after iatrogenic reduction to twin pregnancies. The multifetal pregnancies (three fetuses (2); four fetuses (5); five fetuses (2); six fetuses (2); eight fetuses (1)) were reduced by ultrasound guided transabdominal injection of potassium chloride into the fetal hearts. MSAFP was measured immediately before reduction at eight to nine weeks gestation and at subsequent visits at 10 to 12 weeks, 15 to 17 and 19 to 21 weeks of gestation. Ultrasound examinations performed at each visit demonstrated that complete

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resorption of the dead fetuses occurred 8 to 12 weeks after reduction. MSAFP was also measured in 13 singleton and 11 twin pregnancies achieved after *in vitro* fertilisation (IVF) and embryo transfer; in each case, MSAFP was measured on five occasions between eight and 21 weeks gestation.

Results

In both singleton and twin IVF pregnancies, MSAFP increased exponentially with gestation [$\log_{10}$ (singleton MSAFP + 9) = 0·720 + 0·051 × gestational weeks, SD = 0·101, r = 0·905, $P < 0·0001$ and $\log_{10}$ (twins MSAFP + 9·5) = 0·664 + 0·069 × gestational weeks, SD = 0·162, r = 0·865, $P < 0·0001$] and the mean concentration in twin pregnancies was significantly higher (mean difference = 1·67 SD, SE = 0·26, $t = 6·56$, $P < 0·0001$).

In the multifetal pregnancies, data were expressed as the number of standard deviations (SD) by which values differed from the normal mean in IVF twin pregnancies. The mean MSAFP before reduction was significantly higher than in the IVF twins (Fig. 1: mean difference = 1·08 SD, SE = 0·31, $t = 3·48$, $P < 0·01$), and there was a significant association with the original number of fetuses (Fig. 2: r = 0·764, $P < 0·05$). Similarly, at the first two visits after reduction (10–12 and 15–17 weeks), the mean

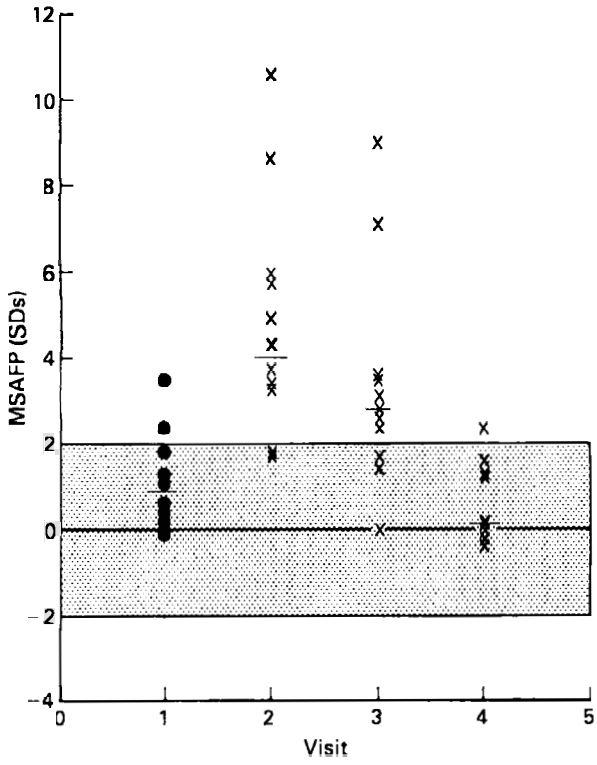

Fig. 1. Individual values of maternal serum alpha-fetoprotein (MSAFP) in multifetal pregnancies before (●) and after (×) embryo reduction to twins expressed as standard deviations (SD) from the normal mean for gestation of twin pregnancies achieved after *in vitro* fertilisation.

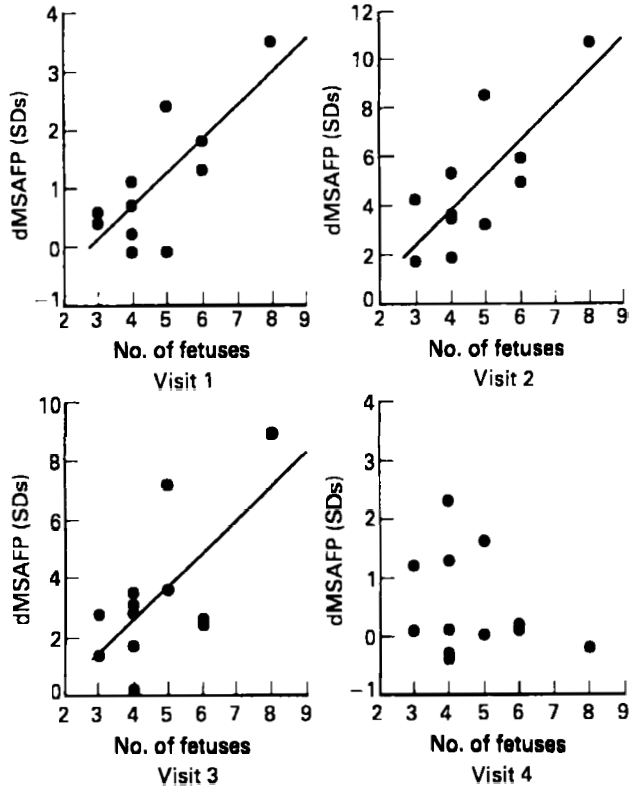

Fig. 2. Association between number of fetuses and dAFP (deviation from the normal mean for twin pregnancies (expressed in SD) before embryo reduction (visit 1) and on subsequent visits.

MSAFP was significantly higher than in IVF twins (mean difference = 4·73 SD, SE = 0·76, $t = 6·26$, $P < 0·001$ and mean difference = 3·35 SD, SE = 0·71, $t = 4·74$, $P < 0·001$, respectively), and levels were significantly associated with the original number of fetuses (r = 0·772, $P < 0·05$ and r = 0·667, $P < 0·05$, respectively). At the fourth visit (19 to 21 weeks), the mean MSAFP was not significantly different from IVF twins (mean difference = 0·49 SD, SE = 0·25, $t = 1·94$), and there was no significant association between levels and the original number of fetuses (r = 0·284).

Discussion

The finding that in multiple pregnancies maternal serum alpha-fetoprotein increases in proportion to the number of fetuses is not surprising since the origin of alpha-fetoprotein in the maternal serum is the fetus. Transfer of alpha-fetoprotein to the maternal circulation is achieved either directly from the fetal circulation across the placenta, or by absorption from the amniotic fluid.

Following the iatrogenic death of fetuses in multifetal pregnancies, there was an increase in MSAFP which persisted for at least eight weeks. Subsequently, MSAFP decreased and by 12 weeks following reduction the levels were within the normal range for twins. This temporary rise in MSAFP may be the consequence of mechanical disruption in the feto-maternal barrier during the re-

duction. Although this would be consistent with the rise in MSAFP that is well described in association with invasive techniques, such as chorion villus sampling, in multifetal pregnancy reduction care was taken to avoid puncture of the placentae of the surviving fetuses. Therefore, the high levels of MSAFP are unlikely to be the consequence of disruption in the feto-maternal barrier and chronic leakage from the live fetuses to the mother across the placenta; the half-life of alpha-fetoprotein in the maternal circulation is only four to five days (Sappälä & Ruoslahti 1973). Furthermore, there was a significant association between MSAFP and number of dead fetuses.

The most likely explanation for high MSAFP following reduction is increased concentration of alpha-fetoprotein in the amniotic fluid due to tissue breakdown from the dead fetuses; MSAFP returns to the normal range 8 to 12 weeks after the reduction because by this time there is complete resorption of the dead fetuses. Previous studies have reported high levels of alpha-fetoprotein in the amniotic fluid of twin pregnancies after the spontaneous death of one of the fetuses (Bass *et al.* 1986; Streit *et al.* 1989) and in multifetal pregnancies after reduction (Grau *et al.* 1990).

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Endometrial hyperplasia and adenocarcinoma during tibolone (Livial®) therapy

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Tibolone (Livial®, Organon, Oss, The Netherlands) is a synthetic steroid [(7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one] which exhibits oestrogenic, progestogenic and androgenic activity (van der Vies 1987). It is given continuously, without cyclical progestogen, for the relief of menopausal symptoms (Joint Formulary Committee 1993) without a return to withdrawal bleeding (Genazzani *et al.* 1991). We report on the first series of women with endometrial pathology diagnosed whilst on tibolone therapy.

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Subjects and methods

Clinical presentations, management and histological diagnoses are summarised on Table 1. The six women were aged 52 to 73 years (mean = 60·2 years) and had been postmenopausal for five to 23 years (mean = 12·7 years). They had been prescribed tibolone for seven to 18 months (mean = 12·3 months) at the time of their first appointment at an outpatient clinic. All had been referred because of single or repeated episodes of postmenopausal bleeding of between one day's and three weeks' duration. Cases 1 to 3 had received no previous hormone replacement therapy, Cases 4 and 5 prior treatment with Prempak-C® (Wyeth, Maidenhead, UK), and Case 6 unopposed oestrogens for 15 years followed by 1 year of cyclical oestrogen/progestogen prior to tibolone therapy.