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Declining incidence of ectopic pregnancy in a UK city health district between 1990 and 1999

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BACKGROUND: On the basis of clinical impression that the number of cases of ectopic pregnancy seen in the City and Hackney Health District, London, was changing, a retrospective study of the years between 1990 and 1999 was carried out. METHODS: From the histopathology databases, cases of ectopic pregnancy and early pregnancy failure were identified. The number of deliveries at The Homerton Hospital was obtained from the Labour Ward register; the number of terminations of pregnancy and the number of fertile women was obtained from the Office for National Statistics, UK. RESULTS: There were 73 cases of ectopic pregnancy in 1990 rising to 96 in 1991 and then a fall to 52 cases in 1999. In terms of ectopic pregnancy per 100 deliveries, per all known pregnancies and per 1000 fertile women per year, there was a peak in 1991 and a fall to 1999. With regard to relative incidence per deliveries and per all known pregnancies, these falls were significant ($P < 0.05$). In 1991, there were 2.4 ectopic pregnancies per 100 deliveries, falling to 1.6 in 1999, a 33% fall. The reasons for this large decline are uncertain. CONCLUSIONS: There has been no change in patient population, diagnostic aids used or management protocols for patients with ectopic pregnancies.

Key words: ectopic pregnancy/relative incidence changes

Introduction

Ectopic pregnancy is defined as the implantation of a fertilized ovum outside the cavity of the uterus. It is of considerable medical importance since it is associated with an increased risk of maternal death (Stationery Office, 1998), sterility and problems in any subsequent pregnancies (Job-Spira *et al.*, 1996). Ectopic pregnancy is also one of the main reasons for emergency admission to hospital, and investigations such as ultrasound scans, pregnancy tests and diagnostic laparoscopy have resource implications. Although no data are available from the UK, it has been estimated that in the USA in the 1980s the cost was about one billion dollars per year (Washington and Katz, 1993). The problem with epidemiological studies of extrauterine pregnancies is associated with its natural history which may be observed, or pass unrecognized, because of spontaneous resolution, and therefore not be observed. The result is that any calculation can be distorted by artefacts such as improved detection with the increasing use of laparoscopy, transvaginal ultrasonography, highly sensitive urine pregnancy test kits and quantitative serum human chorionic gonadotrophin assays (Brennan, 1997; Ankum, 2000).

The choice of denominator used can also give rise to artefact. The three commonly used denominators are the number of births, the number of pregnancies and the number of women of reproductive age (i.e. 15–44 years). Births provide the most accurate denominator as figures can usually be derived from public records, but pregnancies may be more correct since ectopics present at a time when the rates of miscarriage and elective pregnancy terminations are substantial and possibly should be included in any quoted figure. Since miscarriage is not a registerable event, these figures may be difficult to measure accurately. The earlier recognition of pregnancies with the availability of over-the-counter urine pregnancy test kits, and thus increased recognition of earlier pregnancy loss, will influence such comparisons of incidence (Cuckle and Murray, 1997). Figures based on the number of women of reproductive age are influenced by the fertility rates and contraceptive practices of the populations under scrutiny. In England and Wales national data have been published. Using official statistics on a routine 10% sample of hospital discharges (Beral, 1975), the incidence per 1000 registered pregnancies, excluding illegal abortions and miscarriages, increased throughout the study period from 3.2 per 1000 pregnancies in 1966 to 4.3 in 1972. This corresponds to a rate of 2.8 and 3.7 per 10 000 women aged 15–44 years. There have been numerous publications on the increasing incidence of ectopic pregnancy since the late 1970s. In the UK, a doubling over the period from 1977 to 1986 has been reported (Dimitry and Morcos, 1990), and a similar increase has been reported in the Scottish Highlands (Kok *et al.*, 1989).

Many studies have tried to explain these rises, citing causes such as improvements in diagnosis, but also the possible

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association with the incidence of pelvic inflammatory disease (Stray-Pedersen 1996; Low *et al.*, 1999; Kamwindo *et al.*, 2000) or the change in maternal age distribution and the increased incidence of ectopic pregnancy in older women (Nyboe Andersen *et al.*, 2000; Rajkhowa *et al.*, 2000). There are, however, fewer papers reporting a decline in ectopic pregnancies in the 1990s.

We have previously studied the relative incidences of ectopic pregnancy in the City and Hackney Health District and have reported some of the highest ectopic pregnancy relative incidences in the world literature (Irvine *et al.*, 1994). On a clinical impression that there has been a decline in the number of ectopic pregnancies seen in the City and Hackney Health District, we carried out a retrospective study to look at these variations from January 1, 1990 to December 31, 1999.

Materials and methods

To study ectopic pregnancy relative incidences, we first identified the number of histologically diagnosed ectopic pregnancies for each year between 1990 and 1999. The histopathology database at St Bartholomew's Hospital stores a record of specimens received by the department and encodes the diagnosis to the System of Nomenclature of Pathology (SNOP) coding system. Text phrases added to the report are encoded by computer algorithm using a translation table. The data include patient identification, source of specimen plus topographical, morphological, aetiology and functional codes where appropriate. Errors in translation are written to an error file corrected by the pathologist and added manually to the database. Some data are lost in this process, but more usually when the codes are unusual or new to the system. Data are retrieved by laboratory staff using searches written with Datatrieve (Digital) software. In order to look at the number of spontaneous pregnancy failures, we also searched the database for products of conception over the same timescale. In the period of study, there were two hospitals in the City and Hackney Health District which admitted emergency gynaecological cases: St Bartholomew's Hospital and The Homerton Hospital, Hackney, which is the only maternity unit in the Health District. In 1992 the Accident and Emergency Department at St Bartholomew's Hospital closed and patients were diverted to the Accident and Emergency Department at The Homerton Hospital. From The Homerton Hospital Labour Ward register, we extracted the number of deliveries for each year over the same period.

Information on the number of pregnancy terminations and the number of fertile-aged women (defined as aged 15–44 years) was obtained from the Office for National Statistics. Due to administrative changes, after 1992 the figures for termination of pregnancy in City and Hackney were combined with those of Newham and Tower Hamlets, and given as numbers for East London and City. We calculated that the 'Hackney terminations' accounted for ~41% of the total number over the previous 2 years. Hence from 1993 we estimated the number as 41% of the total terminations of pregnancy. The number of women delivered on the labour ward was obtained from the monthly figures compiled by the delivery ward staff.

During the study period there were no unit protocols for the diagnosis and management of women with suspected ectopic pregnancies. There was no facility for the quantative measurement of β-human chorionic gonadotrophin (β-HCG). All patients who gave a history suggestive of ectopic pregnancy, or who had abdominal or pelvic signs, or were haemodynamically unstable, underwent diagnostic laparoscopy. During the study period no patient suspected of having an ectopic pregnancy was managed conservatively.

Statistical analysis

Individual comparisons of the relative incidences of ectopic pregnancy were made using the χ^2-test. In order to investigate and quantify the linear trend in the relative incidences between 1991 and 1996, logistic regression analyses were carried out using the statistical package Genstat. Thus the deterministic part of the equation was:

$$\ln [p/(1 - p)] = a + bt$$

where p is the proportion of ectopic pregnancies, t is the year and a and b are regression coefficients to be estimated. The all-important parameter is b, which is a measure of the systematic change in the proportions over time. Although the regression analysis was carried out on the logistic scale, for ease of interpretation, the fitted values displayed in Table I are the result of a back-transformation to the original scale of percentages.

Results

In 1990 there were 73 cases of histologically proven ectopic pregnancies identified. This increased to 96 cases in 1991 and then fell over the subsequent years to 52 in 1999. In 1990 there were 3852 deliveries at The Homerton Hospital, with a peak in 1991 at 4045 and a subsequent fall over the following years. This peak in 1991 was also observed with regard to the number of early pregnancy failures as reported by evacuation of retained products of conception. The number of recorded terminations of pregnancy fell from 2244 in 1990 to 2052 in 1992 and, based on theoretical calculations, to 2179 in 1998. The number of fertile women (aged 15–44 years) remained relatively stable during the period 1990 to 1997, the last year for which figures are available. Table II gives pregnancy/demographic data.

We calculated the ectopic pregnancy relative incidences in the three standard ways. In terms of ectopic pregnancies per 100 deliveries, the incidence in 1990 was 1.9, peaking at 2.4 in 1991, and dropping to 1.6 in 1999. The peak in 1991 was also seen in all known pregnancies, being 1.42 in 1991 and falling to 0.84 in 1998. Expressed per 1000 fertile-aged women per year, the figure for 1991 was 2.56, declining to 2.32 in 1997 (see Table II).

Table I presents the relative incidences of ectopic pregnancies calculated in two ways; as percentages of deliveries at The Homerton Hospital and as percentages of total pregnancies. Individual comparisons using the χ^2-test suggested that there were some significant differences in the incidence of ectopic pregnancies in different years. Thus the incidence as a percentage of deliveries in 1991 was significantly greater than that in 1996 ($P < 0.006$), 1995 ($P < 0.04$) and 1994 ($P < 0.017$). The data from 1991 through to 1996 were subjected to a logistic regression analysis and provided statistical evidence of a systematic decline in the relative incidences over these years. This trend was evident for both the representations of ectopic pregnancy, as a percentage of deliveries and as a percentage of total pregnancies. The incidence, together with the fitted curves, are displayed in Figure 1.

Discussion

The ectopic pregnancy relative incidence can be described in one of three ways. The first and simplest way of reporting the

Table I. Incidences of ectopic pregnancy as percentages and the fitted values from the logistic regression

	Year									
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
As % of										
Deliveries	1.90	2.37	2.16	2.15	1.58	1.68	1.49	2.09	1.44	1.57
Fitted values	*	2.39	2.17	1.97	1.79	1.63	1.48	*	*	*
As % of total										
Pregnancies	1.12	1.42	1.29	1.30	0.94	1.01.	0.89	1.23	0.85	*
Fitted values	*	1.43	1.30	1.18	1.07	0.97	0.88	*	*	*

The parameter b was estimated as -0.098 ± 0.029 ($P < 0.02$) when the ectopic pregnancies were expressed as a percentage of deliveries at The Homerton Hospital, and as -0.099 ± 0.028 ($P < 0.02$) when expressed as a percentage of total pregnancies. The statistical significance indicates a systematic trend (see Figure 1). The regression coefficient of –0.098 corresponds to an average reduction, in each year, by some 9.3% of the current value.

Table II. Pregnancy/demographic data: City and Hackney Heatlh District

	Year									
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
No. of deliveries at The Homerton Hospital	3852	4045	3711	3535	3488	3582	3819	3782	3816	3956
No. of terminations of pregnancy	2244	2184	2052	1902*	1973*	1958*	2071*	2055*	2179*	N/A
No. of early pregnancy failure specimens	341	415	362	340	394	379	434	388	438	477
No. of ectopic pregnancies	73	96	80	76	55	60	57	79	55	52
No. of all known pregnancies	6510	6740	6205	5853	5910	5973	6381	6304	6488	N/A
No. of fertile women (15–44 years) in Hackney ×1000	38.7	37.5	37.7	37.0	36.5	36.0	35.2	34.0	N/A	N/A
Ectopic pregnancy: relative incidences										
No. per 100 deliveries	1.9	2.4	2.2	2.1	1.6	1.5	1.4	2.1	1.4	1.3
Rate per all known pregnancies	1.12	1.42	1.29	1.30	0.94	0.88	0.89	1.25	0.84	N/A
Rates per 1000 fertile women	1.54	1.92	1.68	1.66	1.67	1.67	1.62	2.32	N/A	N/A

*Theoretical calculation.
N/A = not available.

ectopic pregnancy is to calculate this as number of ectopic pregnancies per 100 or 1000 deliveries. Although the easiest to calculate, this methodological approach has weaknesses in that in areas with a high termination rate, the ectopic pregnancy per delivery will be increased. The second way is to calculate the number of ectopic pregnancies per all known pregnancies. The numerator is ectopic pregnancies, and the denominator is the number of ectopic pregnancies, number of women undergoing spontaneous pregnancy failure (ERPC specimens), number of termination of pregnancies carried out and the number of deliveries. When expressing ectopic pregnancy per all known pregnancies, there is an unknown number of women who miscarry at home and never attend hospital. Thus, although we can never accurately record all pregnancies, these inaccuracies occur in all studies using 'all known pregnancies'. A third way is ectopic pregnancies per 1000 fertile-aged women per year. The last two methods are less often quoted, as the data are more difficult to collect.

In a previous study in the City and Hackney Health District, we reported some of the highest rates of ectopic pregnancies. We identified 106 cases of ectopic pregnancies and 200 controls and found significantly higher numbers of Afro-Caribbean women, and women who had had a previous termination of pregnancy. There was, however, no significant difference with regard to spontaneous pregnancy failure (Irvine *et al.*, 1994). The controls were women who were picked at random from those who delivered on the labour ward during the study period. Due to the selection of pregnant women as controls rather than non-pregnant women, the conclusions drawn must be guarded (Weiss *et al.*, 1985). Others have also commented on the merits of using pregnant or non-pregnant controls in studies of ectopic pregnancy. In a meta-analysis of risk factors for ectopic pregnancy, where the risk factors studied reduced the chances of conception, the odds ratios were higher if pregnant rather than non-pregnant controls were used (Ankum *et al.*, 1996).

Our study shows a significant fall in ectopic pregnancy, relative incidence with time. It is surprising that such a fall should have occurred as there has been no apparent change in our patient population during this time. Also quantative β-HCG assays were not available, and patients were not managed expectantly. Although in later years a few cases were

Figure 1. Plot of the relative incidence of ectopic pregnancy, calculated in two ways.

managed laparoscopically by either salpingectomy or linear salpingostomy, our protocol was to send all tissue samples for histological analysis. There was no protocol for the use of systemic methotrexate and from review of cases, only three cases were identified who were treated successfully with methotrexate. The number of ectopic pregnancies may even have been expected to rise due to the increased activity in the local assisted reproduction unit.

The possibility was considered that closure of the Accident and Emergency Department at St Bartholomew's Hospital, and other changes in the provision of acute services in the East End of London, had resulted in ectopic pregnancies being treated elsewhere. Review of the total numbers attending the remaining Accident and Emergency Departments does not, however, suggest any appreciable change in flow of patients into or out of the District. Health Authority data also demonstrate no appreciable change in the number of patients seen and treated.

There have been other recent publications reporting a fall in ectopic pregnancy rates, although not as substantial as ours. The changes in ectopic pregnancy rates may reflect the way in which the data are collected. In an American study (Anonymous, 1995), a 2 year period from 1990 to 1992 was investigated. Based on data from hospital discharge summaries, the rate was 11.4 per 1000 reported pregnancies in 1990, 10.0 in 1991 and 10.6 in 1992. However, when those patients with the diagnosis of ectopic pregnancy who were treated as an outpatient were included, the rate in 1992 rose to 19.7 per 1000 reported pregnancies. Outpatient ectopic pregnancies accounted for 47% of all cases. In our study, all patients with histological proven ectopic pregnancy were treated as inpatients.

An important risk factor for ectopic pregnancy is pelvic inflammatory disease, which may be caused by *Chlamydia trachomatis* infections which may be asymptomatic (Skjeldestad *et al.*, 1989). Women with subclinical disease may not attend genito-urinary clinics, though suffer damage to their Fallopian tubes (Robertson *et al.*, 1988). A large study from Sweden (Egger *et al.*, 1998) looked at screening and treatment of *Chlamydia* and rates of ectopic pregnancy over a period from 1985 to 1995. They reported an overall ectopic pregnancy rate of 1.8% of all known pregnancies. In women aged 20–24 years there was a highly significant correlation between ectopic pregnancy and chlamydial infection. This correlation was weaker with age and not significant after the age of 35 years. They concluded that, in young women, treating *Chlamydia* considerably lowers ectopic pregnancy rates.

In the population of our study there is no widespread chlamydia screening programme in place, although *Chlamydia* swabs may be taken in genito-urinary clinics. There was no change in the policy for prophylactic antibiotics in the busy pregnancy termination clinics in the City and Hackney Health District in this period.

Falling ectopic rates have also been reported in Finland (Makinen, 1996), with a rise and then steady decline from a peak in 1987 of 176 cases per 100 000 women to 155 per 100 000 in 1994. The reason suggested was the post-war baby boom cohort effect. Females born just after the war experienced an epidemic of pelvic inflammatory disease in the early 1970s and, as a result of tubal damage, ectopic pregnancies in the 1980s. In our study the peak and fall occur many years later.

It is possible that our results could be explained in the same way as the Swedish study (Egger *et al.*, 1998) reported. With the fear of a widespread epidemic of AIDS in the UK many resources were used on health education programmes to promote the message and practice of safe sex. Apart from

reducing the spread of the HIV virus, safer sex would reduce pelvic inflammatory disease, which would reduce the ectopic pregnancy rate. We feel that the practice of safe sex cannot explain the fall in ectopic pregnancies seen, as there was no significant fall in overall pregnancies, termination of pregnancies or deliveries during our study.

The systematic differences reported in this paper cannot be explained by random variation, and are likely to be multifactorial. Further research is required to identify the reasons for the changes in ectopic pregnancy, which is still a major cause of maternal morbidity and mortality.

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