Is there a relationship between treatment for infertility and gestational trophoblastic disease?

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BACKGROUND: The aim of the study was to record the incidence of treatment for infertility prior to development of gestational trophoblastic disease (GTD). METHODS AND RESULTS: A retrospective analysis was undertaken of 231 consecutive women receiving chemotherapy for persistent GTD at Weston Park Hospital, Sheffield, from 1991 to 2001. Three patients in this group had received treatment for infertility prior to their molar pregnancy. In a control group of 226 patients not requiring treatment for persistent GTD, four had had treatment for infertility just before their molar pregnancy, and in a further control group of 208 ‘normal’ pregnancies, eight patients had had treatment for infertility prior to conception. CONCLUSION: We conclude that we can demonstrate no relationship between infertility treatment and subsequent development of GTD.

Key words: clomiphene/GTD/hydatidiform mole/infertility/IVF

Introduction

Trophoblast cells are derived from the embryo and are responsible for the formation of the placenta. Gestational trophoblastic disease (GTD) is a spectrum of disorders, ranging from hydatidiform mole to choriocarcinoma and placental site tumour. The incidence of GTD in the UK is approximately 1.5 in 1000 live births. A variety of risk factors have been associated with its aetiology, including ethnic origin, age, diet and oral contraceptives (Hancock et al., 1997), but no mechanism of causation has been established.

The number of births arising as a consequence of fertility treatment has risen dramatically over the past 20 years. If during gametogenesis and fertilization fertility treatments alter the normal products of conception, there could be an association with GTD, and indeed anecdotal case reports have documented GTD in pregnancies arising as a consequence of assisted conception. There are reports of GTD following clomiphene citrate therapy (Wade, 1980; Mor-Joseph et al., 1985), IVF (Tanos et al., 1994; Makhseed et al., 1998), gamete intra-Fallopian transfer (van de Geijn et al., 1992; Manase et al., 2000) and ICSI (Petignat et al., 2001). Petignat et al. (2002) identified all published reports, and concluded that while there was no added risk of gestational trophoblastic tumours, since multiple pregnancies are more likely to occur the overall risk of molar disease may be increased. However, these are such rare events that prospective study is not possible.

Sheffield is one of only three centres in the UK for the management of GTD, and has records of all patients registered and treated for GTD since 1973. This provided us with a unique dataset to investigate whether there is a relationship between infertility treatment and GTD.

Materials and methods

At this centre, 5.2% of women diagnosed with GTD required chemotherapy. This was a retrospective case–control study involving two control groups. The main study group consisted of 231 consecutive patients who had received chemotherapy for persistent GTD at Weston Park Hospital between 1991 and 2001. For the control groups, we looked at two populations: those who had had GTD but had not required chemotherapy, and a group of healthy women who had no history of GTD. We selected the registration records of every 20th woman diagnosed with GTD between 1991 and 2001 (226 patients), and 208 randomly selected healthy controls who had delivered normally between 1991 and 2001 on the maternity unit of the Jessop Hospital for Women, Sheffield, UK.

The following data were recorded, when available, from the records: age, parity, gravidity, history, cause and treatment of infertility, and type of molar pregnancy.

Result

Patients with persistent GTD (n = 224)

Nine (4%) patients had a history of infertility; their ages ranged from 24 to 48 years (median 30). This was higher than that of the treated population as a whole (27 years).
Five of the infertile patients had received fertility treatment. As a result of treatment, two patients had successfully conceived and had proceeded to have normal full-term deliveries. They have therefore been excluded from the analysis. Two patients developed molar pregnancy following treatment with clomiphene, one following IVF. Of these patients, two (aged 25 and 33 years) had had primary infertility and one (aged 48 years) secondary infertility (with three previous normal children by the same partner). All molar pregnancies were ‘complete’.

Presentation and management of those women with persistent GTD showed no differences from the treated group as a whole. All patients responded to chemotherapy and are currently alive and well. Three women have subsequently conceived successfully, without further treatment for infertility.

**Patients not requiring treatment for persistent GTD**

In this group of 226, three (1.7%) had received treatment for infertility just before their molar pregnancy. All of these patients (ages 28, 38 and 40 years) had had primary infertility. In all cases the treatment was IVF and the molar pregnancy was ‘partial’.

**Normal pregnancies**

In this further control group of 208 normal pregnancies, eight patients (aged 29–40 years, median 34) had had treatment for primary infertility prior to conception. In seven cases treatment was with clomiphene alone, and in one case, IVF.

**Statistical analysis**

The crude and age-adjusted odds ratios according to previous treatment for infertility are shown in Table I. There were no significant differences between the groups.

**Discussion**

A variety of risk factors have been implicated in GTD, but the aetiology remains uncertain. Viral infection, poor nutrition, defective germ cell, prior pregnancies, maternal age, and genetic and environmental factors all have been mooted. Of these, maternal age has consistently been identified as an important risk factor. Age-specific incidence reports usually reveal a ‘J-shaped’ curve, with teenagers having a higher incidence and women over 40 years having a dramatically higher incidence. These are all potential confounding factors in our analysis. We have been able to show that the obstetric histories of patients and controls were similar. Age-adjusted odds ratios showed no significant differences across the groups.

Amongst the patients treated for GTD, nine (4%) had a history of infertility. Current data suggest that primary infertility affects 15% of couples in the UK. There is no quoted figure for the proportion of pregnancies arising in couples with a history of infertility, so it is difficult to know whether the figure for the group of patients with persistent GTD differs from that of the general population.

In Italy, a case–control study was performed on 188 patients with GTD and 410 obstetric controls (Parazzini et al., 1991). Patients tended to be nulliparous more frequently than controls. The risk was also greater in women reporting spontaneous miscarriages. A history of difficulty with conceiving was associated with odds ratios of 2.4 and 3.2 for complete and partial mole, respectively. Fertility treatment was not reviewed separately. In our study we were not able to obtain full histories of previous infertility, except in those patients with persistent GTD, where the incidence was 4%, seemingly lower than that in the general population.

In most other respects, the patients in our study with previous infertility appeared typical of the treated GTD population as a whole. The only further difference noted was a higher median age, although this is to be anticipated in patients with a history of difficulty with conceiving. Our figures confirm the good prognosis of GTD treated within a specialist centre. All patients are alive and well, and three have subsequently conceived despite the previous history of infertility. These figures provide further encouragement for women who have received chemotherapy for GTD and wish a further pregnancy.

With the increasingly widespread use of infertility treatments and the fact that these are more likely to give rise to multiple pregnancies, the overall risk of developing GTD might be increased, particularly so for clomiphene-only induced pregnancies and perhaps less so for IVF, where current policies mean that only embryos selected from chromosomally normal fertilized eggs are replaced. There have been several studies of infertility treatment and subsequent development of cancer (particularly ovarian) (Rossing et al., 1994; Mosgaard et al., 1997; Venn et al., 1999), but none commented on the incidence of GTD.

Amongst 58 pregnancies involving 148 fetuses conceived as a consequence of IVF (Makhseed et al., 1998), one hydatidi-form mole was reported. It is difficult to interpret this as any

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### Table I. Previous treatment for infertility in patient groups: crude and age-adjusted odds ratios

<table>
<thead>
<tr>
<th>Patient groups</th>
<th>Previous treatment for infertility (%)</th>
<th>Crude odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Normal deliveries (n = 208)</td>
<td>8 (3.8)</td>
<td>200 (96.2)</td>
<td>1</td>
</tr>
<tr>
<td>GTD, no chemotherapy (n = 226)</td>
<td>3 (1.3)</td>
<td>223 (98.7)</td>
<td>0.34 (0.09–1.32)</td>
</tr>
<tr>
<td>GTD, chemotherapy (n = 231)</td>
<td>3 (1.3)</td>
<td>228 (98.7)</td>
<td>0.33 (0.08–1.29)</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age.

*Baseline.
more than a chance occurrence. In our study looking at the converse situation (i.e. is treatment for infertility commoner in patients who have GTD), infertility treatment (be it clomiphene stimulation or IVF) was not a frequent predisposing finding.

A recent analysis of published case reports conducted by Petignat et al. (2002) explored whether ovulation inducers, e.g. clomiphene, are a risk factor for persistent trophoblastic tumour. Whilst fertility drugs were not identified as having tumorigenic effects, the authors suggested that, as multiple pregnancies are more likely to occur, the overall risk of molar disease may be increased.

In summary, currently there are little more than case reports suggesting an association between GTD and infertility, and its treatment. Our findings suggest no such relationship, certainly in terms of its treatment, even when adjusted for maternal age. The limitations of this study are that it is retrospective and the patient numbers are relatively small. We were also unable to establish from the case notes the underlying cause of the infertility in our control patient populations, as this information was either unrecorded or the cause was unknown. However, this was a comprehensive study in that 97% of consecutive patients from 1991 to 2001 with persistent GTD and valid control populations were assessed, and, because of the limited sample size, the medical histories of these patients could be researched in detail. In those patients who had received infertility treatment before their molar pregnancy developed, three with complete moles, who developed persistent disease, and three with partial moles, who did not, IVF had been used in one and three cases, respectively. These numbers are far too small to allow valid assessment of the relative impacts of clomiphene alone and IVF in GTD. However, recurrent GTD after IVF has been described (Pal et al., 1996) suggesting the possibility of an oocyte defect predisposing to abnormal fertilization.

In conclusion, our data do not confirm a potential association between infertility, its treatment and GTD. We would suggest that to investigate this further, details of infertility and its treatment be collected at the time of GTD registration.

Acknowledgements
We would like to thank Professor William Ledger (Infertility Centre, Jessop Wing, Sheffield, UK) for his support and advice with this research.

References

Submitted on October 7, 2002; resubmitted on August 13, 2003; accepted on October 9, 2003