Neurofibromatosis type 1 and sporadic optic gliomas

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Aims: To compare the natural history of sporadic optic glioma with those associated with neurofibromatosis type 1 (NF1).

Methods: Optic glioma cases were identified using both the Manchester Children’s Tumour Registry (CTR) and the North West Regional NF1 Database (NF1DB), with detailed information on natural history available from the former (in 34 of 36 cases identified).

Results: A total of 52 cases over a period of 41 years were identified. From the 34 whose natural history was known, almost all (n = 31) were symptomatic, with mean ages of presentation of 4.5 and 5.1 years for NF1 and sporadic cases respectively. The majority (n = 22) presented with visual impairment, seven of whom were blind in at least one eye. Sporadic cases were over twice as likely as NF1 to have visual impairment. Recurrence occurred in 12 patients. Fewer NF1 patients died as a direct result of their optic glioma, but overall mortality and 5 and 10 year survival rates between the two groups were similar. All five primary (non-metastatic) second central nervous system (CNS) tumours occurred in NF1 cases, two of these following radiotherapy.

Conclusions: Symptomatic sporadic optic gliomas presented with impaired vision more frequently and were more aggressive than NF1 optic gliomas. Only optic glioma cases with NF1 were at risk of developing a second CNS tumour. Aggressive treatment of sporadic optic gliomas and early surveillance of NF1 optic gliomas may be required. The use of radiotherapy in these children requires further clarification.

Neurofibromatosis type 1 (NF1) makes up 90% of the genetic disorders known clinically as the neurofibromatoses. It has a prevalence of about 1 in 3000, making it one of the most common genetic disorders. NF1 is inherited in an autosomal dominant manner and gene penetrance is such that almost all cases show sufficient evidence of the disorder to allow diagnosis in childhood. Complications of NF1 provide a more sinister slant to this otherwise relatively benign condition. One of the most notorious complications is that of the central nervous system (CNS) tumour. Optic nerve gliomas were initially reported in less than 5% of NF1 cases, but this was before the advent of computed tomography and magnetic resonance imaging.

More recent estimates from longitudinal studies using modern neuroimaging techniques have put the prevalence between 11% and 19% of NF1 cases, although higher estimates have come from retrospective analyses of referral clinics. As the occurrence of other CNS tumours is thought to be well below 5%, this makes optic glioma the most common CNS tumour to complicate NF1. The natural history of optic gliomas has been increasingly studied in recent years, but it is not clear if these tumours produce significant morbidity or are relatively indolent. Some studies have found the former, but the majority have found the latter and do not see a case for screening or monitoring. However, this may depend on adequacy of treatment, and treatment itself is not without risk.

The discrepancy in natural history may relate to differences in study design, with prospective studies picking up more non-progressive asymptomatic tumours. Some have found that the presence of NF1 in children with optic glioma confers a protective benefit. We have therefore used retrospective data to establish the natural history of optic gliomas and whether NF1 related cases require a different clinical approach to sporadic ones. This also enabled assessment of the overall prevalence of mainly symptomatic optic gliomas in a large population based register of NF1 patients.

PATIENTS AND METHODS

This study was carried out in the North West of England (population 4 million). Patients were identified from two sources: the North West Regional NF1 Database and the Regional Children’s Tumour Registry (CTR).

The NF1 Database (NF1DB)

This consisted of 501 patients by study day. All had been diagnosed by clinical geneticists as part of a regional genetic register. The diagnosis of NF1 was made in accordance with the National Institutes of Health Consensus Criteria. All affected NF1DB cases identified had their clinic notes re-evaluated to provide information concerning their optic gliomas. Unfortunately, those 16 cases only identified via the NF1DB and not the CTR could not be used in the final analysis. This was because of lost notes, unavailable notes, or incomplete information in the notes, either because of failure to attend follow up or lack of relevant detail in the case notes as regards the natural history of the glioma.

The Children’s Tumour Registry (CTR)

This details children under 15 years of age, resident in the North West region, and referred to the main paediatric centres for tumour management. Information is available from 1954 onwards and consists of typed case notes detailing events from the first presentation of the tumour. A search for optic gliomas included the headings “juvenile astrocytomas” and “neurofibromatosis—tumours not otherwise specified” to ensure as many cases as possible were identified. All relevant details about the diagnosis of both optic glioma and possible NF1 were taken from the case notes and other available

Abbreviations: CNS, central nervous system; CT, computed tomography; CTR, Children’s Tumour Registry; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; NF1DB, North West Regional NF1 Database
There was relatively little delay in reaching a diagnosis once the indication was clear what the indications were for scanning in these cases, both being incidental findings on CT or MRI. Although it is not known how many children presented with visual disturbance, occurring in seven cases (41%); two children presented with at least one blind eye. A further four children presented with proptosis. Developmental delay and symptoms suggestive of raised intracranial pressure each occurred in five cases; endocrine disturbance occurred in four (obesity in three, gigantism in one). Only two gliomas were asymptomatic at diagnosis, both being incidental findings on CT or MRI. Although it is not clear what the indications were for scanning in these cases, one was found to have infiltrating cerebellar masses, the symptoms of which presumably brought him to medical attention.

Diagnosis
There was relatively little delay in reaching a diagnosis once the child had presented, the mean time being just over six months. The mean and median ages of diagnosis were 5.0 and 4.0 years respectively. Diagnosis was based on either radiological (9/17) or histological (8/17) evidence.

Treatment
A total of 11 children received specific treatment for their glioma: either surgical excision of part or all of the glioma (7/17) or radiotherapy (4/17). In one of the children treated with radiation, there was a period of abnormally excessive growth during the following year. He went on to develop an asymptomatic recurrence and a cerebellar pontine angle schwannoma 17 years later. Another case had a recurrence at the age of 12, six years after radiotherapy; he died of multiple intracranial tumours, aged 21. The other two appeared not to have had any untoward complications of cerebral irradiation. One of the children initially treated surgically developed a cerebellar astrocytoma at age 10, which was irradiated. Two years after this, his vision began to deteriorate and a recurrent optic glioma was diagnosed at age 17. Follow up information is lacking for one treated and one untreated case. For those on whom we have such data, five of the 10 treated were dead by study day compared with two of five untreated.

Complications
Four gliomas recurred with new symptoms, three following radiotherapy (two, six, and 17 years later), and the other nine years after surgery. A further child who actually died from an axillary neurofibrosarcoma was found to have an incidental chiasmal glioma 17 years after his initial glioma was irradiated. Two children developed endocrinological disorders following glioma diagnosis. One underwent excessive growth from the age of 8, a year after he had received radiotherapy. The other child, who was female, had had radiotherapy for an optic glioma at the age of 7, and was then diagnosed with glioma recurrence at the age of 14 following investigation of primary amenorrhoea. She later developed epilepsy, which by the time she was 36 was described as “uncontrolled”. A further child, whose glioma was initially excised when she was aged 1, developed aqueduct stenosis, a recognised complication of NF1, at the age of 7. This was complicated by hydrocephalus, and despite shunt insertion she died a few days later. Complications were not inevitable and seven children had no further serious problems. Of these, two had been treated surgically, two with radiotherapy, and three had not had specific therapy.

Second tumours
Five children (29%) with NF1 went on to develop second primary CNS tumours, all of which were intracranial and occurred between seven and 32 years from initial treatment. Two of these five occurred in cases treated with initial radiotherapy. One of these was the aforementioned boy who died aged 24 from an axillary neurofibrosarcoma and was found to have, in addition, both a cerebellopontine neurilemoma (schwannoma) and a chiasmal glioma. He had received radiotherapy at the age of 7. Two of the five also suffered with recurrent optic gliomas. Only one of the five appeared to survive his second tumour (a cerebellar astrocytoma), through a combination of radiotherapy and surgery which he received in 1977 at the age of 10. It may be of note that two years after this treatment his vision began to deteriorate and he went on to have further radiotherapy for a recurrent optic glioma in 1984.

Mortality
Overall there was a 47% mortality rate among the 15 of 17 NF1 patients with an optic glioma whose survival was recorded. However, of these seven deaths only two were directly attributable to the optic gliomas. The remaining causes of death were intracranial neoplasia (n = 3), the neurofibrosarcoma (n = 1), and the girl with aqueduct stenosis who had a shunt inserted to drain her hydrocephalus and who died from bilateral subdural haemorrhaging following a fit postoperatively.
Survival
The 5 and 10 year survival rates from first presentation probably give the most realistic idea of the severity of an individual child's condition. These are 77% and 67% respectively, with two outcomes unknown and three cases not applicable (being diagnosed within 10 years of study day).

Location
Further subanalysis using site of glioma was conducted. Using the categories intraorbital (that is, chiasm spared) and chiasmatic (that is, chiasm with or without one or both optic nerves involved), 10 children had chiasmatic gliomas. In addition, two had “bilateral gliomas”, but no reference to the chiasm was made. Four chiasmatic and both bilateral cases presented with visual symptoms, five chiasmatic and one bilateral had endocrine abnormalities, and both asymptomatic patients were chiasmatic. Only one recurrent glioma appeared to have involved new territory, initially affecting the left optic nerve. Nine years after glioma excision and two years following radiotherapy (for a cerebellar tumour), the optic glioma recurred in the chiasm. Of the 10 with definite and initial chiasm involvement, three received radiotherapy, three were excised, and four were left untreated. Information regarding survival in these cases is complete for only five, two of whom died within 10 years of diagnosis (giving a 10 year survival rate of 60%).

Sporadic optic gliomas
Distribution
Of the 17 cases without a diagnosis of NF1, eight were male and all were white Europeans. Three children presented over the age of 10, being 11, 12, and 13. The youngest presented at 3 months with apparent visual symptoms and hypercalcaemia, but was not diagnosed until 12 months old.

Presentation—age
The mean and median ages of presentation were 5.1 and 5.0 (range 0.25–13) years respectively. Only two patients had initial symptoms predating presentation by greater than a year. One had poor growth for probably two years prior to presentation, the other had various endocrine symptoms starting about 15 months earlier. A further five children had a 12 month history of symptoms at presentation, four of these being visual in nature and one having symptoms of raised intracranial pressure.

Presentation—symptoms
The most common presenting symptom was again visual disturbance (15/17 or 88%), with five of these having one blind eye. Proptosis (7/17), endocrine disturbance (5/17, of which two had precocious puberty), and raised intracranial pressure (5/17) were also common, with two cases having nystagmus. Only one case was asymptomatic and picked up via a routine eye check that revealed optic atrophy. Despite no presenting symptoms and receiving radiotherapy, he still went on to develop a blind eye.

Diagnosis
Time to diagnosis from first presentation was just under nine months, with mean and median ages of diagnosis being 5.8 and 5.0 years respectively. Most cases were diagnosed on biopsy (11/17), the remainder either seen on scan (4/17) or directly visualised at craniotomy (2/17).

Treatment
A large majority of these children (14/17) received specific treatment. Most underwent surgery alone (8/17), four had radiotherapy alone, and two children had both kinds of treatment. One of those surgically treated went on to have radiotherapy for recurrence 12 years later and had a second recurrence five years after that. Of the six who initially received radiotherapy, three went on to have a recurrent glioma (four, four, and 23 years later). Six of the 12 treated for whom we have follow up information were dead by study day, compared with two of the three who were untreated.

Complications
A minority (6/17) of sporadic gliomas failed to show disease progression, four having had their tumour excised, one having had radiotherapy, and one having been untreated. Four gliomas recurred. Of these, two may have had a second recurrence. The first was a girl treated initially at 16 months with radiotherapy who then developed bilateral nerve gliomas at age 7, for which she was treated surgically. She died at the age of 10 following an acute right middle cerebral artery infarct, and was found on postmortem examination to have a chiasmal glioma. It is not clear if this was remnant tumour from the previous surgery or true recurrence. The other child had his glioma excised at the age of 4, and was then treated with radiotherapy for its first recurrence at the age of 16. He had a second recurrence at the age of 21, which was untreated and from which he died. The same boy had required shunt insertion at the age of 11 to drain hydrocephalus. Endocrine dysfunction occurred in two cases, one with growth hormone deficiency and one with secondary amenorrhoea. Both had received radiotherapy, respectively, 9 and 14 years previously.

Second tumours
None of the sporadic gliomas appeared to develop another primary CNS tumour, although one boy who was diagnosed on biopsy at the age of 11 months died five months later and the cause of death given was “cerebral tumour”. Most likely this referred to the known glioma as there was no postmortem examination.

Mortality
Of seven deaths, five were definitely directly related to the optic glioma; one other had a fatal complication at the time of her second glioma recurrence in that she sustained a stroke at the age of 10. The final death was a result of a fall from a bike, but no further information is available. Hence, overall mortality was approximately 44%. The five year survival rate at study day was 80%, with one case discounted because of diagnosis after 1991. This fell to 57% for 10 year survival rate, with a further case discounted because of diagnosis within 10 years of study day.

Location
Six sporadic cases involved the chiasm. Four presented with visual symptoms, one had endocrine symptoms, and one was asymptomatic. Three received radiotherapy, two were untreated, and one was excised. Ten year survival for these six cases was 67%.

Comparative analysis
Table 1 presents a comparative analysis of the patients. The gender and racial distributions in our study were similar for sporadic and NF1 optic gliomas. Mean and median ages at presentation, time from presentation to diagnosis, and age at diagnosis were not significantly different between the groups, although sporadic gliomas tended to occur later in all three categories. Two cases in each group recalled symptoms beginning over a year before they presented to the medical profession. Five further sporadic cases noted symptoms starting about a year previously, four of these visual in nature.

One sporadic and two NF1 gliomas were asymptomatic. Of the remaining 31 gliomas, significantly more sporadic (15/16 or 94%) than NF1 (7/15 or 47%) presented with visual symptoms (p = 0.01). A total of seven sporadic (41%) and four NF1 (24%) cases presented with proptosis. Fewer numbers...
presented with endocrine symptoms, raised intracranial pressure symptoms, and focal neurology, and these were evenly distributed between the groups. Both glioma types presented with a variety of symptoms, with 16 sporadic gliomas producing 39 different symptoms, and 15 NF1 gliomas producing 31 symptoms. Definitive diagnosis was made mainly by histological examination, but there was a tendency to rely on imaging alone for NF1 related tumours (table 2).

Treatment approach favoured surgical excision over radiotherapy approximately twice as often in both groups. Twice as many NF1 than sporadic gliomas were left untreated (6 v 3). Despite this, there was a non-significant trend towards fewer NF1 patients dying specifically of their glioma than their sporadic counterparts (2 v 6; p = 0.22). This contrasts with absolute mortality and 5 and 10 year survival rates which are remarkably similar (respectively 44%, 80%, 58% for sporadic; 41%, 70%, 57% for NF1).

The overall glioma complications rate was similar for the two groups. However, visual symptoms were significantly more common among sporadic cases, as was mortality from the glioma. There was a trend towards chiasmatic involvement in NF1 cases (10 v 6). Symptoms and treatment type were similar in kind and number, except for a propensity of NF1 cases to have endocrine disturbances on presentation (5 v 1). The only two cases of bilateral optic nerve involvement were in NF1 children.

(Note: All p values refer to probabilities calculated using Fisher’s exact test).

| Table 1 | Comparisons of NF1 and sporadic gliomas for presentation, diagnosis, and complications |
|-----------|---------------------------------|------------------|-----------------|-----------------|-----------------|
| Presentation and diagnosis | NF1 cases | Sporadic cases |
| Asymptomatic | 2 | 1 |
| Visual: non-blind/blind | 5/2 | 10/5 |
| Proptosis | 4 | 7 |
| Raised intracranial pressure | 5 | 5 |
| Developmental delay | 5 | 3 |
| Endocrine | 2 | 1 |
| Epilepsy | 2 | 1 |
| Space occupying symptoms | 1 | 2 |
| Age at presentation in years—mean | 4.47 | 5.11 |
| Age at presentation in years—median | 4 [1-14] | 5 [0.25-13] |
| Recurrence | 5 | 4 |
| Non-CNS tumour | 1 | 0 |
| Intracranial neoplasm | 5 | 0 |
| Hydrocephalus | 0 | 1 |
| Endocrinological | 2 | 2 |
| Epilepsy | 1 | 0 |
| Death | 2 | 6 |
| None | 7 | 6 |

| Table 2 | Investigation on which diagnosis was based |
|-----------|---------------------------------|-----------------|-----------------|-----------------|
| Diagnostic tool | NF1 cases | Sporadic cases |
| Radiological | 9 | 4 |
| Histological [+/- radiological] | 8 | 11 |
| Macroscopic evaluation (surgically) | 0 | 1 |
| Radiological with macroscopic confirmation (surgically) | 0 | 1 |

DISCUSSION

Optic gliomas account for less than 5% of childhood brain tumours. Their prevalence in the general population is thought to be around 1 in 100,000. The estimated prevalence of neurofibromatosis in patients with optic gliomas ranges from 10% to 70%.

From our population, the most accurate estimate of prevalence looks at the number of NF1 related cases from the CTR alone, as using NF1DB cases would introduce selection bias. This gives a population based value of 18/36 or 50%.

In patients with NF1, the lifetime risk of developing an optic glioma has generally been found to be between about 10 and 20%, although estimates range from under 5% to as high as 28%. In our NF1 database, the prevalence was 5%. Although we lack sufficient data on the reasons for scanning the group of children with NF1 from which the 25 gliomas were identified, it is likely that the majority were symptomatic in order to merit special investigation. Indeed, only two cases were recorded as not having symptoms attributable to an optic glioma at diagnosis. Hence, our figures are likely to reflect prevalence of symptomatic rather than all gliomas.

Particular significance has traditionally been attached to chiasmatic involvement of optic gliomas. In contrast to previous studies we found a preference towards chiasm involvement in NF1 but not in sporadics, and identified cases of isolated nerve gliomas causing precocious puberty, suggesting compression of the hypothalamus might not be solely a manifestation of chiasmal involvement. There was no clear evidence that location affected either management or survival in either group. Nor was there evidence that treatment altered long term outcome, although this is bound to be affected by selection bias, the more aggressive tumours probably being more often treated but also probably having a worse prognosis. Although chemotherapy is a promising new addition to therapeutic options, in contrast to the cases in our study predating the chemotherapy era.

Nine of our cases had a lag of a year or more between first symptoms and diagnosis, suggesting insidious growth. However, seven of these were sporadic cases where the index of suspicion would be expected to be low. Nonetheless, visual symptoms and mortality directly caused by the glioma were significantly more common among sporadic cases. This
suggests that sporadic glomas are more aggressive than their NF1 counterparts. Despite this, absolute mortality figures and 5 and 10 year survival rates were very similar. The reason for this disparity is the high preponderance of fatal second primary CNS tumours in patients with NF1. Thus, five NF1 children with optic glomas developed an intracranial neoplasm (aged 10–34 years). Conversely, no sporadic case was definitely diagnosed with a second CNS tumour. The propensity of second CNS tumour development in NF1 optic glomas has been noted before, and the NF1 gene has been putatively considered tumour suppressant, although only the other direct comparative study of NF1 and sporadic optic glomas did not identify any second malignancies. These findings go against the prevailing attitude that CNS tumours in NF1 regress or are indolent and hence do not require intervention.

Whether the presence of an optic gloma in NF1 children is in itself a marker of tumour susceptibility was not specifically tested by this study. It would require for comparison a group of NF1 patients who developed any other type of tumour and who did not have evidence of an optic gloma. It has been suggested that CNS tumours are specific to those NF1 cases with, as opposed to without, optic gloma. In conjunction with our finding of CNS tumours being specific to optic gloma cases with, as opposed to without, NF1, it could be extrapolated that a dual diagnosis of NF1 and optic gloma is the critical factor for CNS tumour development.

One of the five NF1 children with a second CNS tumour was a boy who later died from an axillary sarcoma at the age of 24. He was found on postmortem examination to have an incidental chiasmal gloma and a cerebellopontine angle schwannoma. This latter tumour may have been related to radiation exposure as its presence contrasts sharply with the absence of other schwannomas on the NFIDB or in population studies of NF1. Our study found that three of the five NF1 children receiving cranial irradiation for a CNS tumour developed further intracranial tumours: an optic gloma, a posterior fossa tumour, or a combination of these. They occurred as long as 17 years after treatment in the case of recurrent gloma and 18 years after treatment in the case of a second CNS tumour. Three of the six sporadics who were initially irradiated developed a recurrent gloma, from a total of only four sporadic first recurrences (see table 3). Three of five irradiated NF1 cases went on to develop another CNS tumour, compared with only two of the remaining 12 not irradiated; this contrasts strongly with the fact that none of the six irradiated sporadic cases developed second CNS tumours. It may be that the presence of NF1 is necessary for second tumour development in irradiated patients with optic gloma. Taken in conjunction with the findings of Cappelli et al of a much higher rate of cerebrovascular complications in irradiated NF1 as opposed to sporadic optic glioma cases; this underlines the need for caution over the use of radiotherapy in these NF1 children.

The only previous study to specifically compare these types of optic glioma concluded that clinical differences existed between the two groups which should “dictate separate concerns in their follow up.” In particular, while precocious puberty, the main presenting endocrine abnormality, was exclusive to the NF1 group, symptoms of raised intracranial pressure and nystagmus occurred only in sporadics. Although in our study both cases presenting with nystagmus were sporadic, we found that almost equal numbers of children in the two groups presented with symptoms of raised intracranial pressure or endocrine abnormalities, and neither of the two children with precocious puberty had NF1.

In conclusion, these data suggest that NF1 related optic glomas are less aggressive than their sporadic counterparts. They are less often aggressively treated, but still less likely to recur or shorten life expectancy. Nonetheless, they produce the same constellation of symptoms and are still responsible, from an early age, for much morbidity and mortality through both visual loss and in particular second CNS tumour development. The implications for management are twofold. Firstly, an aggressive management approach directed at sporadic optic glomas should be considered in line with improvements in therapeutic efficacy given the higher mortality directly attributable to these tumours. Secondly, in young children with NF1, we agree with the North American consensus statement of 1997 that serial ophthalmological examinations should be carried out in NF1 from an early age if we wish to be able to detect and treat early optic glomas. For practical reasons the target age group could be limited to those under 6 years old as most cases were diagnosed by this age in our and previous studies. However, follow up of identified cases with particular attention to second CNS tumour development should be mandatory. This expectant management strategy with recommendations for treatment is part of an international study under the auspices of the International Society for Paediatric Oncologists.

Table 3 Subsequent occurrence of second CNS tumours, recurrence of optic gloma, or both among all patients who ever received cranial irradiation

<table>
<thead>
<tr>
<th>Tumour event</th>
<th>Irradiated NF1 cases (n=5)</th>
<th>Irradiated sporadic cases (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second CNS tumour only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent and second CNS tumour</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent tumour only</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>No recurrent or second tumour</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: second recurrences are excluded.

REFERENCES

Feeding infants of diabetic mothers

In general, breast feeding protects against later obesity and diabetes. Infants of diabetic mothers have an increased risk of later obesity and glucose intolerance. It might be thought, therefore, that breast feeding might protect the infants of diabetic mothers from these later developments but the milk of diabetic mothers contains more glucose, insulin, and energy than that of nondiabetic mothers, especially in the early neonatal period, and could be harmful. A study in Berlin (Andreas Plagemann and colleagues. Diabetes Care 2002;25:16–22) has suggested that early breastfeeding by diabetic mothers may have adverse consequences.

Between 1980 and 1989 112 infants of diabetic mothers (83 type 1 diabetes, 29 gestational diabetes) were followed up at a clinic in the then East Berlin. The mothers were encouraged to breastfeed and supplements of banked donor breast milk were given when deemed necessary. Infants who took more of their mother’s milk were more likely to be overweight at age 2 years (proportions overweight in first, second, and third centiles for weight of mother’s breast milk taken in the first week were 5/37, 11/38, and 14/37). The weight of mother’s milk taken in the first week correlated directly with relative body weight at age 2 years whereas the weight of banked donor breast milk taken correlated inversely with relative body weight at age 2 years. Similar associations were found between amounts of mother’s and donor milk taken in the first week and the 120 minute blood glucose concentration on oral glucose tolerance testing at 2 years. The risk of impaired glucose tolerance at age 2 years was inversely related to the amount of donor breast milk taken.

Breast feeding by diabetic mothers may increase the risks of later overweight and glucose intolerance in their infants. (The authors of this article are careful to point out that in their opinion the advantages of breastfeeding still outweigh the disadvantages even for diabetic mothers.)