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Prescription drug use during pregnancy and risk of childhood cancer – Is there an association?

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ABSTRACT

In economically developed countries up to 90% of women are prescribed medications, including vitamins and supplements, during pregnancy. Whilst a number of adverse health outcomes in their offspring have been related to prescription drug use, associations with childhood cancer are less clear and most investigations have been reliant on maternal self-report. With a view to providing new insight we investigated maternal prescription drug use and risk of childhood cancer primary care medical records collected as part of the United Kingdom Childhood Cancer Study, a national population-based case–control study conducted between 1991 and 1996. There was evidence that mothers of children with acute lymphoblastic leukaemia (OR 1.36, 95% CI 1.14–1.63), medulloblastoma (OR 1.79, 95% CI 1.00–3.22) and Wilms tumour (OR 1.79; 95% CI 1.05–3.04) were more likely to have been prescribed iron when compared to mothers of controls. In addition, systemic anti-infectives were positively associated with acute myeloid leukaemia (OR 1.58, 95% CI: 1.05–2.38) and rhabdomyosarcoma (OR 1.80, 95% CI 1.03–3.16), and analgesic use (NO2B) was positively associated with Hodgkin lymphoma (OR 5.02, 95% CI 2.16–11.82) and neuroblastoma (OR 1.99, 95% CI 1.07–3.69). Whilst our findings suggest that maternal use of antibiotics, iron, and nervous system drugs during pregnancy may be associated with some childhood cancer subtypes these associations need to be confirmed elsewhere. Unravelling the mechanisms that may underpin these associations is complex and research is needed to determine whether they are directly related to the drugs themselves, or the illnesses for which they were prescribed.

1. Introduction

Although strict guidelines govern the use of prescription medications during pregnancy, up to 90% of women in economically developed countries are prescribed at least one drug during this time [1–6]. Some medications including anti-emetics, antacids, vitamins and supplements, as expected, are given more frequently in pregnancy [1,2,4,5] with others, such as anti-infectives, also commonly prescribed for acute conditions [5]. In addition, medications essential for controlling long-term health conditions such as epilepsy and depression continue to be prescribed [5,6], with the benefits outweighing possible teratogenic effects.

Maternal exposure to medications during pregnancy has been linked to an array of adverse reproductive outcomes including low birth weight, congenital abnormalities, as well as physical and development delays [7–9]. One of the most striking outcomes to date has been the association between diethylstilbestrol and the rare clear cell adenocarcinoma of the vagina in young women [10]. This observation by Herbst and Ulfelder in 1971, coupled with accumulating evidence that childhood cancers may originate in utero, has led to continued speculation that maternal prescription drug use during pregnancy may impact on disease risk in their offspring. However, although there have been several reports of associations between drugs such as vitamins/supplements and antibiotics and childhood cancer, many findings are inconclusive and/or contradictory [11–20]. In addition, since most studies have been based on self-reported data, both recall and reporting biases impact on interpretation.

With a view to providing insight into the relationship between maternal prescription drug use during pregnancy and subsequent childhood cancer, we analysed data obtained from maternal medical records collected as part of a national population-based study of childhood cancer carried out in the United Kingdom.

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2. Patients and methods

Comprehensive details about the conduct of the United Kingdom Childhood Cancer Study (UKCCS) and its ethical approvals are described elsewhere (www.ukcss.org) [21]. In brief, children under the age of 15 years diagnosed with cancer between 1991 and 1996 in England, Wales and Scotland were eligible. For each case, two controls, were randomly selected from primary-care population registers and individually matched to their corresponding case by sex, month and year of birth, as well as region of residence.

At interview, parents were asked to consent to allow access to their primary care (general practice) records, as well as those of their child. For mothers, all information contained within these routinely compiled health records, from 10 years prior to, and 1 year after the index child's birth, were subsequently abstracted onto specifically designed forms by centrally trained staff [22]. The data collected included all diagnoses recorded contemporaneously by the general practitioner (primary care physician), as well as signs and symptoms recorded at the same time; referrals to hospital consultants and other specialists, results of all investigations; and detailed information on all medicines and treatments prescribed. Data collection and entry were structured around dated "events" (general practice consultation, blood tests, screening procedures, hospital admission, etc.) with all data being entered centrally under the supervision of experienced primary care nurses. Coding of drugs and diseases are key issues in the handling and analysis of such data. Adopting a unified approach facilitates coding, and this has been achieved by using a sophisticated system of computerised "pick-lists" embedded in the data entry programme. Strict quality control procedures, including duplicate data entry of approximately 1 in 4 randomly selected records, were carried out throughout.

All illnesses, symptoms and diagnoses were centrally coded in accordance with the International Classification of Diseases (ICD-10), Tenth Revision [23]. Initially drugs were coded according to a schema based on the British National Formulary (BNF) [24] and subsequently classified into groups according to the World Health Organisations (WHO) Anatomical Therapeutic Chemical (ATC) code. In the present report, analyses were restricted to ATC classes where at least 250 control mothers had a prescription during pregnancy which included the following groups; A (alimentary tract and metabolism), B (blood and blood forming organs), D (dermatologicals), G (genito-urinary system and sex-hormones), J (anti-infectives for systemic use), N (nervous system) and R (respiratory system).

Area-based deprivation scores were derived using standard methods; full details of which have been previously published [25]. In summary, the mother's postcode on the child's birth certificate was used to allocate deprivation scores at birth and categories were derived by dividing the continuous deprivation score for the 1991 census enumeration areas into five equally sized groups, with group one representing the most affluent, and group five the least.

Seven of the 10 UKCCS areas (co-ordinating centres in Birmingham, Cambridge, Leeds, London, Manchester, Oxford and Southampton) systematically collected primary-care records from mothers of cases and controls within their area, but selection policies varied between regions [22]. The targeting policy for mothers' notes was similar to that previously reported for children [22]; with one area aiming to abstract the notes of mothers of all cases and both controls (Oxford) and the remainder of all cases and at least one control – the mother of the first randomly selected interviewed control. In addition, some regions further restricted activity to leukaemia cases and their corresponding controls alone (London) and/or to specific geographic areas within their region (Cambridge, Leeds, London, Southampton). Overall, the GP records for the natural mothers of 1718 cases (83.8% of those targeted) and 2633 controls (64.6% of those targeted) were traced and abstracted, the lower overall control proportion being a reflection of the targeting of only one control per case in some regions. Of these, 1598 (93.0%) cases and 2524 (95.9%) controls had at least one event/visit recorded during pregnancy. With a health-care system free at the point of contact, the vast majority of pregnant women in the UK visit their GP at least once during pregnancy; and notes without a recorded visit/event during this time are likely to

Table 1
Characteristics of cases and controls, United Kingdom childhood cancer study 1991–1996.

	Controls, *N* (%)	Cases, *N* (%)					
		Total cases	Leukaemias	Lymphomas	CNS	Sarcomas	Other cancers[a]
Total	2524 (100)	1598 (100)	873 (100)	114 (100)	231 (100)	125 (100)	255 (100)
Gender							
Boys	1406 (55.7)	883 (55.3)	473 (54.2)	79 (69.3)	108 (46.8)	69 (55.2)	154 (60.4)
Girls	1118 (44.3)	715 (44.7)	400 (45.8)	35 (30.7)	123 (53.2)	56 (44.8)	101 (39.6)
Mean age (SD) at (pseudo) diagnosis	5.8 (4.1)	5.8 (4.1)	5.5 (3.8)	8.9 (4.0)	6.7 (4.0)	7.2 (4.4)	3.6 (3.6)
Year of birth							
1976–1983	844 (33.4)	523 (32.7)	230 (26.4)	72 (63.2)	115 (49.8)	66 (52.8)	40 (15.7)
1984–1990	833 (33.0)	535 (33.5)	314 (36.0)	36 (31.6)	72 (31.2)	33 (26.4)	80 (31.4)
1991–1996	847 (33.6)	540 (33.8)	329 (37.7)	6.0 (5.3)	44 (19.0)	26 (20.8)	135 (52.9)
Birth order							
1	1058 (41.9)	701 (43.9)	380 (43.5)	58 (50.9)	91 (39.4)	58 (46.4)	114 (44.7)
2	932 (36.9)	536 (33.5)	288 (33.0)	30 (25.4)	86 (37.2)	41 (32.8)	92 (36.1)
3	372 (14.7)	242 (15.1)	135 (15.5)	18 (15.8)	38 (16.5)	17 (13.6)	34 (13.3)
4+	162 (6.4)	119 (7.5)	70 (8.0)	9 (7.9)	16 (6.9)	9 (7.2)	15 (5.9)
Deprivation at birth[b]							
(affluent) 1	529 (21.0)	307 (19.2)	177 (20.3)	18 (15.8)	39 (16.9)	22 (17.6)	51 (20.0)
2	553 (21.9)	319 (20.0)	175 (20.1)	27 (23.7)	47 (20.3)	20 (16.0)	50 (19.6)
3	561 (22.2)	330 (20.7)	174 (19.9)	18 (15.8)	51 (22.1)	28 (22.4)	59 (23.1)
4	480 (19.0)	336 (21.0)	177 (20.3)	26 (22.8)	53 (22.9)	30 (24.0)	50 (19.6)
(deprived) 5	393 (15.6)	298 (18.7)	165 (18.9)	25 (21.9)	40 (17.3)	25 (20.0)	43 (16.9)
Missing	8 (0.3)	8 (0.5)	5 (0.6)	–	1 (0.4)	–	2 (0.8)

[a] Includes retinoblastoma, neuroblastoma, Wilms tumour, hepatoblastoma, germ cell tumours and other non-specified cancers.
[b] An area-based measure. Quintiles based on the national distribution of areas by deprivation at birth.