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MATERNAL USE OF MEDICATION AND CHILDHOOD LEUKEMIA

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Table of Contents

Abstract

This thesis explored the association between maternal use of medication during pregnancy and risk of childhood acute lymphocytic leukemia (ALL); specifically, whether use of antibiotics, analgesics, anti-nauseas and/or illicit drugs were associated with an increased risk of ALL in the offspring. All cases of ALL, aged 0-14, diagnosed in Quebec during the period 1994-1997 were identified and matched to population-based controls by age and sex. With an overall response rate of 87%, this resulted in nearly 160 case-control pairs. Information was obtained from parents via telephone interviews, and analyzed using conditional logistic regression. Overall use of medication did not increase risk of childhood ALL (OR=1.15, 95% CI=0.66 – 1.99). Increased risks were observed for illicit drug use in the year prior to birth (OR=2.44, 95% CI=0.66 – 9.00), and for the offspring of women who used pain medication during delivery (OR=1.88, 95% CI=1.05 – 3.31); however, the latter increase was seen for male children only (OR=3.43, 95% CI=1.45 – 8.10).

Cette thèse explore l'association entre l'utilisation de médicaments pendant la grossesse et le risque de leucémie aiguë lymphoblastique; spécifiquement, si l'utilisation d'antibiotiques, d'analgésiques, de médicaments anti-nausées, et/ou de drogues illicites était associé à un niveau de risque augmenté de leucémie aiguë lymphoblastique chez la progéniture. Tous les cas de leucémie aiguë lymphoblastique diagnostiqués chez les enfants de 0 à 14 ans au Québec entre 1994 et 1997 ont été identifiés et assortis à des témoins de la communauté. Étant donné un taux de réponse de 87%, un total de 160 paires cas-témoins ont participé à l'étude. Des informations ont été obtenues auprès des parents par l'entremise d'entrevues téléphoniques. Ces informations ont été analysées en utilisant une régression logistique conditionelle. L'utilisation globale de médicaments n'a pas augmenté le risque de leucémie aiguë lymphoblastique (rapports de cotes 1.15, intervalle de confiance de 95%=0.66-9.00). Une augmentation du risque a été observée avec l'utilisation de drogues illicites un an avant la naissance (rapports de cotes 2.44, intervalle de confiance de 95%=0.66 – 9.00) et pour les enfants chez lesquels les mères ont utilisé des médicaments contre la douleur durant l'accouchement (rapports de cotes 1.88, intervalle de confiance de 95%=1.05 – 3.31). Par contre, cette dernière n'à été remarqué que chez les garçons (rapports de cotes 3.43, intervalle de confiance de 95%=1.45 – 8.10).

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Introduction

Acute lymphocytic leukaemia (ALL) is a devastating disease that affects nearly 250 Canadian children each year. Due to remarkable advances in medical therapy, the probability of surviving childhood ALL has dramatically increased over the past quarter century. Approximately 70-80% of children with ALL currently survive five or more years post-diagnosis. However, even among those who survive, the physical, psychological and emotional burden inflicted upon both the patient and the family can be intense. Therefore, preventing the disease and reducing its overall incidence is equally, if not more, important than successful treatment. Nevertheless, causal factors leading to the development of childhood ALL are basically unknown and, until identified, control and preventive measures cannot be taken.

The primary objective of this thesis is to assess the risk of developing childhood ALL as a result of the use of medication during pregnancy. Exposures encountered during pregnancy are an obvious area of investigation due to the vulnerability of the developing foetus and the accumulating data showing that leukaemia can arise prenatally. As well, certain medications are known to have carcinogenic properties and their use has been shown to be related to cancer in humans. However, the risk of childhood cancer from the use of medication during pregnancy has not been thoroughly examined. If found to increase the risk of childhood leukaemia, the potential for controlling and reducing the incidence of the disease may be substantial. In terms of both monetary and social value, reducing even a fraction of childhood cancer would be remarkable.

Background

Burden of Childhood Cancers

In Canada, approximately 900 children between the ages of 0-14 are diagnosed with cancer each year, or 16 per 100,000 children (1). An additional 400 young adults aged 15-19 develop cancer each year (2). Although survival rates for children with cancer have increased dramatically over the past two to three decades, nearly 200 Canadians under 15 years of age still die each year from their disease (1). Among Canadian children, cancer is the second leading cause of death, after accidents, and results in an annual loss of approximately 13, 500 years of potential life (1).

Childhood vs. Adult Cancers

Unlike adult cancers, which are primarily epithelial, childhood cancers are mainly hematopoietic and embryonal in nature. Childhood cancers are also more histologically diverse than adult cancers and are, thus, classified by morphology as well as topology, while adult cancers are traditionally categorised only by site (3). The international classification of childhood cancers (ICCC) edited by Kramarova (4) is the latest revision of the classification scheme. Within the ICCC, childhood cancers are divided into twelve groups (from highest to lowest age standardised incidence rate (ASIR)): leukaemia, brain and spinal, lymphoma, sympathetic nervous system, soft tissue, renal tumours, carcinoma, bone, germ cell, retinoblastoma, other cancers, and hepatic tumours. Leukaemia, the most common childhood cancer, accounts for over 30% of new cases and 32% of deaths from childhood cancer.

Childhood Leukaemia

Leukaemia, a malignancy of the hematopoietic system, is characterised by the proliferation of abnormal leukemic cells which suppress and replace normal blood cells in the bone marrow (5). Clinical symptoms include infections, fever, abnormal bruising or bleeding and fatigue. Childhood leukaemia is commonly divided into the following major categories: acute lymphocytic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, other lymphoid leukaemia, acute undifferentiated leukaemia, and acute mixed lineage leukaemia (6).

With an ASIR of 48.1 per million, Canada has one of the highest rates of childhood leukaemia in the world, comparable to the USA (approximately 45) and Australia, NSW and Queensland (46.7). Costa Rica has the highest national ASIR (59.4) while Nigeria has the lowest reported ASIR (11.8) (6). The ASIR in Canada is slightly higher than published rates from Western Europe, which generally range from 37-40 cases of childhood leukaemia per million.

Childhood Acute Lymphocytic Leukaemia

Seventy to eighty percent of leukaemia in children is acute lymphocytic (ALL). ALL is the most frequently diagnosed childhood cancer among all industrialised nations, including Canada (7). The ASIR of ALL is approximately 38 per million in Canada; it accounts for nearly a quarter of all cases and 15% of all deaths due to childhood cancer (1).

Over the past 40 years, the annual rate of ALL has increased significantly throughout most of the world. In Britain, the highest increase was found among children aged 1-4; it reached

approximately 1% over the forty-year period (8). In the US, rates of ALL among white children increased from 1973-1990, however, changes in diagnostic procedures may account for some, if not all of this trend (9). In other nations, namely, Puerto Rico, Japan, India and Hong Kong, the incidence of childhood ALL increased by more than 20% over the same time period; again, some of this increase may be due to changes in reporting and/or diagnostic procedures.

Cellular types of ALL

In acute lymphocytic leukaemia, normal bone marrow and lymphatic tissue is replaced by abnormal lymphoid precursors with immunocyte-specific determinants (10). The malfunctioning precursor cells, either B-cell or T-cell in origin, accumulate in the blood-forming tissue while, either simultaneously or prior to leukemic cell replication, normal hematopoiesis becomes impaired.

Thus, ALL is classified by immunologic type: B-cell or T-cell. While B-cells protect the body against bacteria through the production of antibodies, T-cells emit toxins to destroy foreign viruses. Approximately 80% of ALLs are B-cell origin, while the other 20% originate from T-cells. B-cell type ALL can be further divided into early, or common, B-ALL (80%), mature B-cell ALL (~1%), and pre-B ALL (~20%). Early, or common, B-ALL appears more frequently in the industrialised world, while T-cell ALL accounts for the majority of ALLs in Sub-Saharan Africa (7).

Age and Geographic Distribution of ALL

In most industrialised countries, the rate of ALL peaks in children aged 2-4 years. This peak has been apparent since the 1930s and is virtually absent in the developing world (11). In Sub-Saharan Africa, and other developing nations, with the exception of Costa Rica, age at diagnosis is spread fairly even from 0-14 years.

Interestingly, it seems that as countries or populations within countries, become more developed or wealthy their risk profile changes. The high incidence of common ALL along with an early peak, between 2-4 years, corresponds to countries or regions of higher socio-economic status (SES) (7). In Britain, the incidence of ALL is higher in areas of higher SES (7). In the US, the ASIR of ALL among black children is beginning to resemble that found among whites. As well, in Kuwait, a marked early childhood peak of ALL is beginning to emerge. Thus, based on findings from ecological studies there seems to be a consistent relation between SES and risk of ALL, though the factors precipitating the high rates and the early childhood peak of ALL remain elusive.

Risk factors of ALL

As previously stated, little is known about the aetiology of childhood cancer (8) though some factors are strongly suggestive. Beyond elements associated with SES, risk of childhood ALL is higher among white males, children aged 2-5 years, children with certain congenital or immuno-deficient disorders, as well as those exposed to some environmental agents. Still, only *in utero* ionising radiation and some genetic syndromes, such as Down's, are currently considered causal

(12;13), and, together, are estimated to account for only 5-6% of childhood ALL cases (14). The causal factors implicated in the remaining 95% of cases are not clear, although numerous hypotheses have been generated and tested. The following literature review briefly discusses studies that have examined established and suspected risk factors for childhood ALL (see Appendix 1 for a list of factors) along with some proposed biologic mechanisms. This is followed by a more in-depth review of the main exposure of interest -- medication use during pregnancy -- and a discussion of the biologic plausibility that could help explain a positive association.

Genetic Syndromes and Abnormalities

Several genetic syndromes have been shown to be associated with an increased risk of childhood leukaemia (11). For instance, Down's syndrome is usually reported to be associated with a 10-to 20- fold increase in risk of childhood ALL (15). Kleinfelter's syndrome, ataxia telangiectasia, neurofibromatosis, and Li-Fraumeni have also been shown to increase the risk of developing childhood ALL (10;16). However, given that genetic syndromes are quite rare, they account for only a very small proportion of childhood leukaemia cases (11).

Many acquired chromosomal abnormalities have also been found in children with leukaemia (5). Some cases of ALL have been found to express the Philadelphia chromosome translocation, while up to 80% of infant leukaemia show a translocation of the MLL gene at chromosome band 11q23 (12). These findings emphasise the need to combine epidemiologic data with molecular biology when conducting risk assessment research. Subjects with mutations in the genes involved in metabolizing environmental exposures have been shown to be at much higher risk for

developing ALL when exposed to certain environmental factors compared to subjects without the mutations (17-19).

Ionising Radiation

Prenatal exposure to ionising radiation is the other established risk factor for childhood ALL (5). In general, the relative risk of developing ALL after prenatal exposure to radiation ranges from 1.5-1.7 (20;21), though van Steensel-Moll, et al. (22) found that exposure to radiation in the first month of pregnancy increased the risk of ALL in the offspring by a factor of 7.2 (95% CI = 1.2 - 43.7)! As well, postnatal exposure to diagnostic irradiation has been shown to increase the risk of leukemia in some (18;23;24) but not all studies (23;25;26). More recent studies, however, have reported lower risk estimates associated with radiographic exposure during pregnancy (23); these findings may be due to the decline in use and/or the dose applied (27).

Socio-economic status / Infectious hypothesis

As previously discussed, peak incidence of ALL in early childhood seems to reflect socio-economic factors, at least to some extent (5). In general, studies have shown an increased risk of ALL among middle and upper socio-economic classes (28;29), but there are exceptions (30). In addition to lifestyle and access to medical care, other etiologic factors may play a role in the association between SES and childhood leukaemia. In particular, delayed exposure to infectious agents found among smaller families with less crowding, may be associated with the 2-4 year old peak in childhood leukaemia (31;32). More recently, Infante-Rivard, et al. (18) found that markers of early infection (ie., day care attendance, having siblings) were associated with a

reduced risk of ALL. Thus, SES is more likely a marker for varying environmental exposures, rather than differences in genetic or lifestyle factors.

Birth Weight

High birth weight has been reported to be associated with an increased risk of ALL, especially among children diagnosed before four years of age (13;33;34). A birth weight greater than 4000g -- 3500g in certain studies (21) -- seems to be associated with an elevated risk. Cnattinguis, et al. (35) only found an increased risk of ALL among children >=4500g at birth. Still, other studies have found no association between birth weight and risk of ALL (36;37). It has been suggested that high birth weight may increase childhood ALL risk through an overall increase in cell division, perhaps beyond control (5), or simply because heavier babies have a higher number of cells at risk. Furthermore, there is speculation that high levels of insulin growth factor one (IGF-1), an essential hormone in the blood formation process, may contribute to leukemogenesis and has been shown to be positively associated with high birth weight (38). Alternatively, elevated birth weight may be a proxy for other factors, such as SES, which themselves could be responsible for the increase in childhood ALL risk (39).

Maternal Age

Older maternal age has been shown to be positively associated with childhood ALL (13), however, these findings are not consistent across studies (37). Some investigators have found no association between older maternal age (>=35) and risk of childhood ALL; instead they've reported an increased risk among younger (<20 yrs) versus average aged (25-30 yrs) mothers

(34;35). It has been hypothesised that chromosomal abnormalities, especially in the germ cells, which increase with age may affect childhood ALL risk.

Fertility problems

Numerous studies have shown an increased risk of childhood ALL (normally 2-5 times higher) among women with a history of prior foetal loss (13;40;41). Yeazel, et al. (41) found that mothers with a history of one miscarriage were five times more likely to have a child with ALL, while women with two or more prior foetal losses had offspring with an increased risk of nearly 25-fold (95% CI=8.2 - 74.7). Other investigators (21;34;35), however, found no association between foetal loss (>=1) and risk of ALL (OR=1.3, 95% CI = 0.8-2.1). It is likely that prior foetal loss is a proxy for an environmental exposure or inherited genetic defect rather than a direct, causal factor (11).

Hormones (including nausea)

The infamous relation between maternal use of diethylstilbestrol (an supplemental oestrogen) during pregnancy and vaginal adenocarcinoma in the female offspring was first reported in 1971 by two groups of investigators (42;43). Since then, numerous studies have found an increased risk of childhood ALL among mothers who took hormonal treatment for infertility (34;40;44;45). Risk of childhood cancer from other hormonal therapies, including use of oral contraceptives, has been investigated but no consistent increases in risk have been found (46;47).

Nausea during pregnancy, thought to be an indication of elevated levels of maternal oestrogen and human chorionic gonadotrophin (hCG), has also been examined as a risk factor for

childhood cancer (47-49). An increased risk of testicular cancer among the male children of mothers who experienced nausea while pregnant has been found in at least three studies (47;50;51). Henderson et al. reported a 4.0-fold, non-significant increase in risk of testicular cancer in children of mothers who had severe nausea while pregnant. As well, Sanderson, et al. (48), reported that female offspring of mothers who have nausea and/or vomiting during pregnancy may be at an increased risk of breast cancer later in their lives. Still, the occurrence of morning sickness has not been reported to be associated with an increased risk of childhood leukaemia (25;52), ANLL (53), or brain tumours (54). Considering that 50-70% of women report feeling nauseous or experience vomiting during pregnancy (55), the population attributable risk could be important even if the association with childhood leukemia is weak.

Electromagnetic fields

Electromagnetic fields (EMF) are present in all lines carrying electrical current. Although EMFs are too weak to produce ionizing radiation they can affect the activity of components in the pathways that regulate cell proliferation (56). The results of studies examining the association between EMF exposure and childhood leukemia are mixed. The initial case-control study by Wertheimer and Leeper (57) found that risk of death from leukemia was three times higher among families living near powerlines with high versus low magnetic fields. More recent studies have shown both significantly positive (58-61) as well as null or negative (62-67) effects of EMF exposure on childhood leukemia risk. Interestingly, it seems that when EMF is measured indirectly higher risk estimates are found compared to when direct, more sensitive measurements are used (68). Thus, the association between EMF and childhood ALL is likely a proxy for another, related environmental factor.

Occupational and other environmental exposures

Parental employment in hydrocarbon-related and other occupations involving use of chemicals (eg., benzene, petroleum, paints, and other solvents) was hypothesized to increase leukemia risk in the offspring given the findings from adult and animal studies (69). Studies on both paternal (70-72) and maternal (21;22;70;73;74) occupational exposures have found positive associations with leukemia risk, though there are null or inconsistent findings (71;75-77). Though less often examined, maternal occupational exposure to dusts, including metal, organic, and wood dusts (21;70;72;75) as well as employment in the service sector and textiles industries (22;25;71) have also been reported to be associated with significantly increased leukemia risk in the offspring.

Studies on parental occupational exposures to pesticides and risk of childhood leukemia are mixed (21;25;70;71;78), though residential exposure seems to be consistently associated with an elevated risk of childhood leukemia (17;70;79-82). Many pesticides, including organophosphates, have mutagenicity, hemotoxicity, and leukemiogenicity properties (5) which children may be particularly sensitive to (68).

Tobacco

The association between maternal smoking and risk of childhood ALL is not clear (38). Numerous studies have found no association between smoking during pregnancy and risk of leukaemia in offspring (19;21;22;34;35;46;83;84). However, other studies have found a positive relation between parental smoking and risk of childhood ALL (85;86) as well as all cancers combined (87). For instance, Stjernfeldt, et al. (85) found a two-fold increase of ALL and a dose-

response relation among children whose mothers smoked during pregnancy. As well, Infante-Rivard, et al. (19) found children with variants in certain genes involved in the metabolism of polycyclic aromatic hydrocarbons – a common substance in all cigarettes – and whose mothers smoked during pregnancy had a higher risk of ALL. Cigarette smoke does contain many leukaemogenic compounds, e.g. benzene, and transplacental carcinogenic effects have been shown in animal studies. Furthermore, in North America, the proportion of women who smoke while pregnant is relatively high at 20-30% (88-90), thus the population attributable risk could be large if any increase in risk does exist.

Alcohol

Most studies have not found an association between maternal use of alcohol during pregnancy and childhood cancer, including ALL (21;45), AML (91), rhabdomyosarcoma (92), retinoblastoma (93), or hepatoblastoma (94). In fact, some studies have reported significant protective effects from alcohol consumption during pregnancy and risk of childhood leukaemia (19;34;46;95). Still, the possibility of a positive relation between maternal alcohol consumption and childhood cancer cannot be excluded without larger studies employing more sensitive exposure measures, especially as heavy alcohol consumption during pregnancy has been shown to have teratogenic effects on the foetus (5). In the US, approximately 20% of pregnant women consume some alcohol while pregnant (90;96); while the latest Canadian report shows that nearly two-thirds of women have at least one drink during pregnancy (89).

Recreational Drugs

Maternal use of marijuana during pregnancy has been found to be associated with an increased risk of leukaemia (53), brain tumours (97), and rhabdomyosarcoma (92) in the offspring. Increases in risk are normally around 3-fold, yet Robison et al. (53) found an 11-fold increased risk of ANLL among mothers who used 'mind altering drugs' (mostly marijuana) during or just prior to pregnancy. Cocaine use during pregnancy has also been reported to increase childhood cancer risk in the offspring (92;97). However, one study of retinoblastoma found no increase in risk with maternal use of recreational drugs during pregnancy (93).

Maternal use of marijuana may affect the foetus in a number of ways including disruption of cell division, transplacental toxicity, and impairment of the immune system (5). Alternatively, some investigators have suggested that the pesticides used on marijuana plants may be responsible for the increased risk, rather than the drug itself. When used in combination with other drugs -- such as LSD -- congenital abnormalities have appeared in the offspring of marijuana users (53). Cocaine use during pregnancy has also been found to increase the risk of congenital abnormalities in the offspring (92). Furthermore, both cocaine and marijuana have been found to be teratogenic in animal and human studies; thus both have carcinogenic potential (92;98). Reports from Canada and the US estimate that 5-6% of pregnant women use some sort of illicit drug while pregnant (89;90;96).

Maternal Medication

Similar to other potential risk factors, the association between childhood cancer and use of medication during pregnancy has not been extensively studied although transplacental

carcinogensis has been proven (i.e., DES and vaginal adenocarcinoma). In fact, risks associated with drug use during pregnancy in general are not well understood (99) partly because pregnant women are not eligible for clinical trials. And, among the few observational studies that have examined the use of drugs during pregnancy and childhood cancer, the results are often inconsistent.

Overall drug use during pregnancy

Though drug use during pregnancy is often discouraged, a surprisingly high number of women receive prescriptions and take some form of medication while pregnant. Most studies performed during the 1970s and 1980s reported an average of 50-90% of pregnant women received at least one prescription while pregnant, while more recent studies have reported lower values in the range of 35% to 65% (100-102). Thus, it seems reasonable to estimate that close to half of all women use at least one drug while pregnant. Furthermore, results from the US (100;103) show that, overall, women take an average of 1.2-1.3 different types drugs during pregnancy, while the average number of drug types consumed is 2.9 among women who report using medication during pregnancy.

Overall drug use and risk of childhood cancer

van Steensel-Moll, et al. (40) found that overall drug intake during pregnancy was significantly higher among mothers of children with ALL when compared to age- and sex-matched population controls (OR=1.5, 95% CI=1.2 - 2.0). In a cluster analysis, Cocco, et al. (104), also found an increased, though not significant, risk of ALL in the offspring of mothers who used medication while pregnant (OR=4.0, 95% CI=0.6 - 26.3). Moreover, van Duijn, et al. (105), found overall

drug intake during pregnancy increased the risk of acute non-lymphocytic leukaemia (ANLL) in the offspring, but not significantly (OR=1.2, 95% CI=0.7-2.3). However, when comparing mothers of children who died from childhood cancer to mothers of live controls, Gilman, et al. (106), found no increase in risk associated with overall use of medication during pregnancy. In fact, they concluded that risk of childhood cancer from maternal use of medication was secondary to the effect the indicating illness had on the foetus. Finally, although analysis is not complete, preliminary results from a recent German study show no increase in risk of childhood leukaemia associated with the use of medication during pregnancy (107).

Antibiotics

In a review of eighty-nine case-only studies, Satge (108) found that five out of nine mothers who had children with infant leukaemia used antibiotics during pregnancy. Moreover, Infante-Rivard, et al. (109) found a moderate increase in risk associated with maternal use of antibiotics during pregnancy that seemed limited to cases diagnosed before four years of age. Three large case-control studies (two using population-based controls and the other with hospital controls), however, found no association between use of antibiotics during pregnancy and childhood leukaemia (40;45;46;110). Moreover, no association has been found between use of antibiotics during pregnancy and ANLL (53;105), retinoblastoma (93) or rhabdomyosarcoma (92). Still, Gilman et al. (106) did find an increased risk of death from childhood cancer associated with the use of antibiotics during pregnancy. Studies from Europe and the US indicate that between 7-10% of pregnant women report using antibiotics while pregnant (111;112).

Analgesics

Use of analgesics during pregnancy was reported to increase the risk of all cancers combined (106), neuroblastoma (113), and Wilms' tumour (114) in the offspring. However, some studies have found no increase in risk of leukaemia (46), ALL (52), rhabdomyosarcoma (92;115), or brain tumours (116) as a result of using aspirin-type medication during pregnancy. Prescription sedatives, tranquillisers, and narcotic analgesics, on the other hand, have consistently been associated with an increased risk of leukaemia (40;46;52;53;117), neuroblastoma (113;118), and rhabdomyosarcoma (92). The risk of brain tumours associated with maternal use of barbiturates is mixed with some studies showing a positive result (54), and others reporting negative findings (116;119;120). Use of analgesics during pregnancy is likely between 8-10% (96;111;112), though one large European study reported that 17% of women used analgesics while pregnant (121).

Anti-nauseas

Another group of drugs that has received a less than thorough examination is anti-nausea medication, even though approximately 6-10% of pregnant women report using antinauseas while pregnant (102;111). Gilman (106) reported that children who died from childhood cancer were more likely to have been pre-natally exposed to anti-nausea medication compared to population controls. As well, Robison, et al. (53) found an increased risk of ANLL (OR=1.75, 0.98-3.20) and a dose-response relationship associated with the use of anti-nausea medication during pregnancy. A significant increase in risk and dose-response relationship was also shown for astrocytoma (OR=2.0, 1.0-4.1) (97) and retinoblastoma (OR=2.8, 1.2-7.1) (93). Moreover, a non-significant increase in risk of Wilms' tumour was found among women who used antinausea

medication during pregnancy (114). Other studies, however, have found no association between maternal use of antinauseas and neuroblastoma (113), or brain tumours (54;122). Only two published studies have examined the risk of ALL associated with maternal nausea and vomiting; one found no increase in risk with use of anti-emetics during pregnancy (49), while the other did not have sufficient number of exposed subjects to analyse (4 cases vs. 2 controls) (52).

Pain medication during delivery

Use of analgesics, nitrous oxide, barbiturates, general anaesthetic, and other sedatives during labour have been shown to be positively associated with childhood cancer in general (87), leukaemia (37;46;106), lymphoma (123), Wilms' tumour (124), and brain tumours (116;125;126) in the offspring. Still, other studies have found no increase in risk of childhood leukaemia (35;52;87;110), brain tumours (54;127), retinoblastoma (93) or all childhood cancers combined (128) associated with the use of pain medication during delivery. Use of anaesthetic gas during delivery seems to vary across countries from under 3% in Italy to over 30% in Australia (126). In a recent Canadian study, approximately 25% of women reported using anaesthetic gas during delivery (126).

Biologic Plausibility

Heritable factors are thought to account for less than 10% of all childhood tumours (129). Thus, the great majority of childhood cancers are probably sporadic, resulting from exposure to environmental carcinogenic agents that have yet to be identified (130); or, more likely, from the interaction between environmental and genetic factors (17;18;131). Exposure to medication *in utero* may be one of the factors that increases the risk of childhood cancer in the offspring. It has

been shown that nearly all drugs ingested during pregnancy enter the circulation of the conceptus and present a potential hazard to the developing foetus (132). Moreover, maternal exposure to certain drugs and other environmental chemicals during pregnancy are known to cause *in utero* death, birth defects, and other functional abnormalities (133). However, even though transplacental carcinogenesis has been proven, risk of cancer associated with medication use during pregnancy has not been extensively studied (134) and the potential biologic mechanisms which may explain the increase in risk are not clear.

Potential carcinogenicity of medication

Though none of the medications under investigation in this study are known carcinogens, they all have the potential to become embryotoxic and teratogenic during metabolism. Relatively nontoxic xenobiotics, including drugs administered during pregnancy, can be transformed into electrophilic and/or free radical reactive intermediates through bioactivation by embryonic cytochromes such as P450 (135). The reactive intermediates are highly toxic and can cause DNA damage unless mediated by detoxification or macromolecule repair systems. Though some of the damage due to the reactive intermediates may be teratogenic, the potential to also be carcinogenic is tangible. In fact, teratogenesis and carcinogenesis are believed to be allied processes and, depending on the particular agent, mode, and time of action, the outcome will manifest itself either as a cancer or malformation or both (136).

It may also be possible that drugs taken during pregnancy modify the effect of substances associated with increased cancer risk, perhaps by increasing their biologically effective dose, thereby increasing the risk of leukemia in the offspring (113). For instance, aspirin may increase

the effective dose of alcohol (137). Moreover, intrauterine exposure to pharmaceuticals may initiate cells which, if promoted later in life (i.e., post-natally), could result in tumour formation (138).

Susceptibility of the foetus

Foetal tissue is highly susceptible to chemical insults due to its state of rapid cell division, its lack of DNA repair enzymes, and the slow rate of detoxification (39;138). Moreover, the placenta possesses xenobiotic-metabolizing capacity which may increase the concentration of ingested drugs and reactive intermediates in the embryonal and foetal system (139). However, the route of administration and the dose of medication ingested may affect the level of risk placed on the foetus while other factors could counteract the carcinogenic effect of ingested xenobiotics such as ascorbic acid which can inhibit the endogenous synthesis of nitroso compounds in humans (140). The foetus may also be protected to some extent by the maternal detoxification system (141). Therefore, the bioavailabilty of medications taken during pregnancy is unknown and more detailed, sensitive exposure assessment tools are needed to accurately determine the potential increase in risk of childhood cancer associated with drug use during pregnancy.

In summary, the limited findings from studies which have examined the association between maternal use of medication during pregnancy and childhood cancer risk are mixed. However, the proposed biologic mechanisms by which drugs ingested during pregnancy may adversely affect the foetus, including raising its risk of cancer, are reasonable. Not only do the medications under investigation have carcinogenic potential, but the innate susceptibility of the foetus increases the

likelihood of tumour initiation and/or promotion. Moreover, even though pregnant women do not commonly use some subgroups of medications, overall exposure is quite ubiquitous.

Methods

Study Objective

Thus, given the limited and controversial evidence for an association between medication use during pregnancy and childhood ALL risk, as well as the biologic potential which could explain an increase in risk, the objective of this thesis is to examine the relationship between maternal drug use and childhood ALL risk. In particular the following questions will be addressed:

1. Is there an association between maternal use of antibiotics, anti-nauseas, analgesics (including those administered during delivery), and/or illicit drugs during pregnancy and childhood ALL, and;

2. Are other medications used during pregnancy related to childhood ALL risk?

Study Background

Funded by the National Health Research and Development Program (NHRDP) and Fonds de la recherche en santé du Québec (FRSQ), Dr. Claire Infante-Rivard of McGill University, carried out a case-control study of childhood ALL for cases diagnosed between 1980-1993. As part of a distinct and ongoing childhood cancer risk factor study funded by the Laboratory Centre for Disease Control (LCDC), Health Canada, Dr. Infante-Rivard's team is collecting data for cases diagnosed between 1994 -1999. This thesis uses data collected from the latter study which is not yet complete. The childhood cancer risk factor (Aetiology) study is one component of the

Canadian Childhood Cancer Surveillance and Control Program (CCCSCP) within the Cancer Bureau at LCDC. In conjunction with the Treatment and Outcome Surveillance component of the CCCSCP, childhood cancer cases were identified and recruited by the paediatric oncology treating hospitals in Quebec. Age- and sex-matched population controls were identified by the provincial health insurance agency and recruited by the Dr. Infante-Rivards's staff at McGill University. Information about exposure to potential risk factors was obtained from the subjects' parents by McGill staff through a telephone interview. Data were collected on a variety of exposures, including use of medication during pregnancy (see Appendix 2 for a complete list of variables).

NOTE: Please note that although data for approximately 500 cases and controls from Dr. Infante-Rivard's study were made available, it was decided for administrative reasons to only use data acquired through LCDC funding. In addition, although the latter study includes cases diagnosed from 1994-1999, only data from 1994-1997 will be used due to incomplete ascertainment / data validation for the years 1998-1999.

Study Subjects

Leukaemia Cases

Case subjects included all children (0-14) with ALL who were diagnosed at or referred to one of the four hospitals in Quebec that treat children with cancer (see Appendix 3 for a list of participating centres). Tracing cases from these hospitals is equivalent to population-based ascertainment.

To be eligible for the study, case subjects had to meet the following inclusion criteria:

1. Diagnosed with acute lymphocytic leukaemia [ICD-O-2 code: M-9821/3] in Quebec between January 1, 1994 and December 31, 1997.

M-9821/3 includes:

- acute lymphoblastic leukaemia, NOS,
- acute lymphocytic leukaemia,
- acute lymphoid leukaemia,
- acute lymphatic leukaemia.

2. Aged 0-14 at diagnosis.

3. Resident of Quebec at the time of the interview.

4. One parent or guardian with sufficient language skills in either French or English to complete the telephone interview. This was determined by the interviewer upon initial contact.

5. Relation to parent(s) must be biologic; adopted children were not eligible.

6. The household must have had a telephone at the time of the interview.

Population Controls

A randomly selected comparison group of population control subjects, pair-matched to cases by sex and age (± 6mos) in a 1:1 ratio, was identified from the sample provided by the provincial health insurance agency in Quebec (RAMQ). The control group represented the base population from which case subjects emerged, except they had no previous diagnosis of cancer.

To be eligible for the study, control subjects had to meet the following inclusion criteria:

1. At risk of developing cancer at the time and age the case was diagnosed.

2. Must have been a resident of Quebec at the time of the interview.

3. One parent or guardian with sufficient language skills in either French or English to complete telephone interview. This was determined by the interviewer upon initial contact.

4. Relation to parent(s) must be biologic; adopted children were not eligible.

5. The household must have had a telephone at the time of the interview.

Each year, the provincial health insurance agency (RAMQ) was given a distribution list of expected cases in Quebec, divided by sex and age. Ten potential control subjects were then selected for each case by RAMQ and the sample was forwarded to McGill.

Study Procedures

Leukaemia Cases

Case subjects were initially identified and asked to participate in two LCDC projects, concurrently: i) Treatment and Outcome Surveillance and ii) Aetiology (142). Once identified, a research nurse at each hospital recruited the incident cases. Only after subjects had consented to participate were their names given to the project co-ordinator at McGill. The project co-ordinator reviewed the hospital charts for each case to confirm diagnosis. The parent(s) of each case was then contacted by telephone to confirm eligibility and participation, and to set up an interview time.

Population Controls

After the study co-ordinator received the sample of potential control subjects (including address and telephone information) from RAMQ, contact was initiated. The parent(s) of each control subject was initially contacted by telephone to confirm eligibility and request participation. Upon receiving verbal consent, the parent(s) was sent a letter of informed consent to sign and return. A mutually agreeable date and time to conduct the telephone interview was also arranged.

As information from both (living) biologic parents was sought during the investigation, separate interviews were conducted with the mother and father. Regardless of who was contacted first, the interviewer requested information about the location of the other parent to arrange their interview. Parent(s) of case subjects were not contacted until at least four months had passed since diagnosis to allow time for remission to occur. Additionally, parent(s) of deceased cases were not contacted until at least six months had passed since time of death.

Data Collection

Information from case and control subjects was obtained from two sources: medical chart review and self-report. The medical charts provided only a limited number of basic variables, such as diagnosis, age at diagnosis, address information, etc., thus most of the information was obtained by self-report during the telephone interview.

The data collection instrument used during the telephone interview was developed at McGill for a previous case-control study of childhood leukaemia (17). Based on the experience of the prior

study, it was modified slightly by the working group at LCDC. The items in the instrument are primarily nominal and closed-ended, which is considered optimum for collecting reliable and accurate information about drug use during pregnancy (143). Furthermore, interviewers were trained to avoid bias and leading during the data collection procedure, and scripts were developed to help guide the interviewer and to maintain a high level of consistency when obtaining information from case and control subjects. The reliability and validity of some sections of the data collection instrument were tested after the initial case-control study (144). However, the validity of the maternal use of medication section has not been checked.

Ethical Approval

For case subjects, approval to conduct the study was granted by the research ethics boards (REB) of each participating hospitals. Ethical approval was also obtained from the Commission d'accès à l'Information du Québec before the sample of control subjects was acquired. Furthermore, informed consent was obtained from each subject before the interview was conducted.

Study Measures

Outcome Variable

Primary diagnosis of ALL (M-9821/3) was made by the attending paediatric oncologist at each participating hospital. Diagnosis was based on clinical symptoms and histological assessment. The research co-ordinator at McGill University checked the diagnosis of each case as well as the coding scheme used by the hospital. If the oncology department did not use the ICD-O-2 manual, the appropriate conversion was made (i.e., from Birch-Marsden based on ICD-O-1 to ICCC

based on ICD-O-2). Only incident, primary cases of childhood ALL were eligible for the study. Control subjects status was determined by self-report.

Exposure Variables

Main Exposure Variable

During the telephone interview, the subject's mother was asked about medication use during her pregnancy with the index child, as well as in the year prior to conception and during breastfeeding. Frequency of use, reason for consumption, and commercial names of drugs taken were also acquired. To maximise reliability of exposure information, mothers were recruited into the study as soon as possible after the child's diagnosis (median value=0.75 years between diagnosis and interview date). As well, control subjects were matched to cases by date of birth to ensure a consistent amount of time had passed between the pregnancy and the interview.

Only medications that were identified, a priori, as being of interest were analysed. Thus, main exposure variables were limited to the following types of drugs: anti-nauseas, antibiotics, analgesics – including pain medication during delivery – and illicit drugs. Use of medication during pregnancy only -- not prior to pregnancy -- was analysed for all types of drugs except those categorised as illicit. The decision to look at illicit drug use in the year prior to pregnancy was made after use during pregnancy was found to be minimal, and the biologic mechanisms that could explain an increase in childhood ALL risk, even if exposed prior to pregnancy, were plausible.

Confounding Variables

Basic demographic information, including age at diagnosis and sex, was obtained from the hospital medical chart. Information about all other potential confounding variables was gathered during the telephone interview. These include: maternal age at delivery, birth weight, household income at delivery, mother's level of education, use of tobacco and alcohol during pregnancy, xray exposure, prevalence of congenital abnormalities, maternal illness during pregnancy, and incidence and duration of nausea and/or vomiting during pregnancy.

Sample Size and Power

Approximately 45 cases of ALL (aged 0-14) are seen at the four participating hospitals each year in Quebec, or nearly one-fifth of all cases in Canada. Based on available reports from studies accruing cases mostly in the previous decade, it was expected that 40-50% of study subjects would have been exposed to medication during pregnancy, while the proportion would be lower for individual types of drugs. Thus, the number of subjects required to detect a relative risk of 1.8-2.0 at 80% power assuming a background exposure of 0.40-0.50 ranges from 132 to 187 (see Table 1a for exact numbers). However, once exposure levels drop (i.e. for individual medications) only relative risks over 2.5 are detectable with the same number of subjects (see Table 1b for exact numbers). Thus, although the sample size is sufficient to reveal moderate increases in risk from overall use of medication, power to detect small risk increases for individual drug types is quite low with the data presently available for analysis. For instance, power to detect a 50% increase in risk with 180 pairs of subjects assuming a background exposure of 10% is only 24% (α=0.05).

Statistical Analysis

An experienced research assistant at McGill carefully entered the data using built-in safeguards for impossible codes. Frequencies were run on all the variables of interest defined in the *measures* section. The distributions of all variables were observed. No missing values were found and outliers were only detected one or two times due to the fact that the study is not yet complete and the final overall check of the data has not been carried out. Analysis was done with and without the outlying values to determine whether their inclusion affected the overall results.

All dichotomous variables were re-coded 0-1 from 1-2 for ease of interpretation during the modelling phase. Subjects who answered N/A, or not applicable, were moved to the no ('0') category. Those who checked NSP ("ne sait pas" or "don't know") were coded as missing. On one or two occasions, individual answers were changed from 0 to 1 if the subject later responded to a question that indicated the subject had been exposed to, or used, the item. As well, some items listed in the other category were moved into pre-existing categories when appropriate.

New variables were calculated and/or created where required, such as age of mother at delivery, age of child at diagnosis, number of different illnesses/medications/problems during pregnancy, dose of medication used, and number of different congenital abnormalities found in the index child. Certain continuous variables were categorised for ease of interpretation and to observe potential dose-response patterns. These included: age at delivery/diagnosis, weeks of nausea during pregnancy, birth weight, dose of smoking and drinking during pregnancy. Categories

were generally divided into percentiles (e.g. quarters, quintiles, etc.), with an equal number of subjects in each grouping, unless natural categories existed and were of interest for comparison. For instance, age at diagnosis was defined as <2 years, 2-5 years, and >5 years for stratified analysis. As well, birth weight was categorised as normal (3,000-4,000gm), low, or high. Categories for mother's level of education and household income at delivery were predefined in the questionnaire, though some categories were collapsed to keep the number of subjects in each group similar and/or for sake of comparison.

A correlation matrix was run next to explore the relation between the independent variables, including the main exposure variables as well as the potential confounders. If any of the potential confounding variables were highly correlated with any of the main exposure variables, they were not included in the model due to problems of collinearity. As well, if any independent variables were highly correlated with each other, only one was used as a potential confounder during the modelling phase.

Dummy variables were then created for all categorical responses used during regression modelling. If an obvious baseline was not available, the category with the highest number of observations was used as the reference group. To ensure the correct scale was used, the trend and linearity of the categorised variables were checked using logistic regression. If a linear trend was not observed, the categories were either redefined and tested again or a higher order term was tried. In some cases, the normally distributed continuous variable was used a linear relation between the first order categories was found.

Univariate analysis was done next to reveal the association between the exposure variables and childhood ALL risk. Conditional logistic regression and/or two-by-two tables were used to estimate the odds ratio and 95% confidence intervals for each independent variable. Stratified analysis, by child's sex and age at diagnosis, was also performed for the main exposure variables to evaluate the presence of interaction. If the direction of the odds ratio differed between the strata, some level of interaction was assumed and was tested during the modelling phase using the log likelihood ratio. Potential effect modifiers other than the matching variables (e.g., mothers age at delivery, birth weight, type of delivery) were defined a priori based on plausibility and/or use in previous studies and were also tested during modelling. If the addition of an interaction term significantly changed the log likelihood, based on the chi-square distribution at the appropriate degrees of freedom, it was included during the modelling phase and the stratified results were reported. In this case, confidence intervals for the adjusted odds ratios were estimated using the method outlined by Kleinbaum, et al. (145).

Potential confounding was examined through bivariate analysis. Using conditional logistic regression, the adjusted odds ratio was compared to the crude odds ratio for the main exposure variables after the inclusion of each potential confounder according to the change-in-estimate method (146). If the inclusion of the independent variable changed the point estimate by 10% or more, and/or there was a logical association between the potential confounder and maternal use of medication, then the variable was considered during the modelling phase. In a few instances, confounders which did not change the OR by >=10% were retained because they were deemed

biologically important, or they had been repeatedly controlled for in other articles, or it was impossible to separate the effect of two independent variables (e.g., household income and mother's education).

Based on the above analysis, the best model was defined for each main exposure and tested using conditional logistic regression. For each main exposure, the following variables were added one at a time, and then removed sequentially: mother's age at delivery (categorical), birth weight (continuous), household income (categorical) and mother's level of education at birth (categorical and dichotomous), smoking and drinking during pregnancy (Y/N, and dose), x-ray exposure during pregnancy and in the year prior birth (Y/N), prevalence of congenital abnormalities (Y/N and number of different types), illness during pregnancy (Y/N and number of different types), and medication use during delivery (when not the main exposure). As well, an interaction term for the effect modifiers, which were found to be significant during univariate analysis (i.e., child's sex and age at diagnosis), were included in the model. If more than one model for each main exposure was acceptable based on validity considerations, the more precise model (i.e. narrowest confidence intervals) was chosen.

Response Rates

Response rates were very high for both case and control subjects for all four years of the study (see Table 2 for breakdown by year of diagnosis). The overall response rate was 87% for all subjects; oddly it was slightly higher for controls (89%) than cases (85%). This is due to the fact that a number of case subjects refused to participate when initially approached by the data

management nurse at the treating hospital; the McGill team was not involved in the initial recruitment of cases. Once forwarded to McGill University, no further case subjects refused or were lost to follow-up.

Results

Potential confounding variables

The distribution of potential confounding variables can be seen in Table 3. Over 90% of all subjects were white, and 98% of subjects were born in Canada (data not shown). Approximately three-fifths of the subjects were both male and diagnosed with ALL between the ages of 2-5 years. As subjects were matched on age and sex, the proportion of cases and controls in each age/sex grouping are identical.

Though there seems to be no clear difference between cases and controls with respect to birth weight, a higher proportion of controls were found in the lightest category and slighter more cases were in the heaviest weight category. Although the data are not shown, 80% of the deliveries were vaginal; the rest were Caesarean section.

The two variables used to estimate socio-economic status (SES) in this study were household income at delivery and mother's level of education. Again, no clear difference between cases and controls was apparent for either variable. A bi-modal distribution for household income at delivery was seen for cases as a higher proportion were found in the lowest and highest categories and fewer in the mid-range. Controls, on the other hand, showed a normal distribution

across household income categories. The distribution of mother's level of education was normal for both cases and controls, though a slightly higher percentage of case mothers completed degrees/ diplomas at college or university compared to controls.

Mother's age at delivery may also be considered a marker for SES as women in higher SES categories tend to delay childbirth to some extent. In our data set, there were slightly more case than control mothers in the older age groups (> 30 years), though not all subjects were firstborn children.

Interestingly, in our data set, a slightly higher percentage of control mothers smoked cigarettes and drank alcohol during pregnancy than case mothers. Moreover, case mothers who smoked consumed slightly fewer cigarettes than controls. Still, case and control mothers seemed to have smoked for a nearly equal number of trimesters (data not shown). Among mothers who drank alcohol during pregnancy, however, cases consumed slightly more drinks per month than controls.

Exposure to irradiation during pregnancy was slightly more common among case mothers than controls. However, control mothers reported exposure to abdominal x-rays more often than cases, though the number exposed was very small. Interestingly, x-ray exposure in the year prior to pregnancy was more common among case mothers than controls (data not shown); both periods of exposure were explored during modelling.

Another established risk factor, congenital abnormalities, was found to be slightly more common among cases compared to controls in our data set. However, a higher percentage of control subjects had two or more abnormalities, while case subjects were more likely to have only one congenital abnormality. When divided by type of abnormality, no individual category showed a noticeable difference in the proportion of case and control subjects.

Illness during pregnancy was also examined as a potential confounding variable. Case mothers did report being sick more often during pregnancy than controls and they were slightly more likely to have two or more illnesses versus none.

Finally, the proportion of subjects who experienced nausea and/or vomiting in each trimester is shown. Not only were cases in our study more likely to have experienced nausea during pregnancy, but they also had nausea and/or vomiting for a longer duration than control subjects.

Main exposure variables

Approximately 30% of subjects (32.9% of case mothers and 27.4% of controls) took at least one type of medication during pregnancy (excluding vitamins; see Table 4a). An equal number of case and control mothers (21.7%) used only one type of medication versus none, while slightly more cases consumed two or more different types of medication compared to controls (10.2% versus 5.7%).

The number of mothers who used each type of medication is also shown in Table 4a. As previously discussed, many mothers used no medication at all, while a few mothers used some of the medications listed. The medications of interest are highlighted in the table: anti-nauseas were used by more case than control mothers (3.8% vs. 1.3%), as were antibiotics (8.9% vs. 5.1%) and analgesics (3.2% vs. 1.3%). Though illicit drug use during pregnancy was almost nil, more case than control mothers reported using illicit drugs in the year prior to birth (5.7% vs. 2.6%).

Dose of medication used by case and control mothers was also calculated (Table 4b). Case mothers consumed a significantly higher total average number of pills during pregnancy (82.8 pills) than control mothers (61.0 pills), or approximately 2.2 vs. 1.6 pills per day ($p<<0.01$). Again, the medications of interest are highlighted in the table. Case mothers consumed a slightly higher number of anti-nausea pills (7.4 vs. 5.6) and antibiotics (3.4 vs. 2.0) during pregnancy than control mothers. As well, case mothers consumed nearly four times the number of analgesics compared to control mothers (7.9 vs. 2.1), and about double the number of illicit drugs in the year prior to birth (10.6 vs. 5.4).

Though the following medications were not analysed further, it is interesting to note that although diabetes medication was used by nearly the same number of case and control mothers (2 and 3, respectively), the average number of pills consumed during pregnancy was much higher among cases (8.9 vs. 2.5). As well, thyroid medication was not only reported more often among control subjects but the total dose consumed was higher for control compared to case mothers

(5.4 vs. 1.8). The only other medications that were used more often and at higher doses by control mothers compared to cases were fertility hormones, anti-asthmatics, and antacids.

Univariate Conditional Logistic Regression

Univariate conditional logistic regression was used to obtain point estimates and confidence intervals for risk associated with use of medication during pregnancy (see Table 5a). Use of at least one type of medication during pregnancy versus none was associated with a slight but non-significant increase in childhood ALL risk (OR=1.26, 95% CI=0.76 – 2.09). No increase in risk was seen among women who used only one type of medication versus none (OR=1.00, 95% CI=0.58 - 1.72), while children of mothers who used two or more types of medication during pregnancy had a nearly two-fold increase in risk of ALL (OR=1.88, 95% CI=0.80 – 4.42).

When the individual types of medications were modelled, no significant relationship with childhood ALL risk was found. However, a non-significant increase in risk was shown for the previously hypothesised medications, namely, anti-nauseas (OR=3.00, 95% CI= 0.61 – 14.86), antibiotics (OR=2.00, 95% CI=0.75 – 5.33), analgesics (OR=2.50, 95% CI=0.49 – 12.87), and illicit drugs (OR=2.25, 95% CI=0.69 – 7.31). Since the average dose of medication consumed by study subjects was generally quite small, these numbers were not analysed further.

Pain medication used during delivery was analysed next (see Table 5b). Overall, use was significantly higher among case mothers than controls (OR=2.05, 95% CI=1.20 - 3.50). As well, there was significant interaction with child's sex. Among boys, a significant increase in risk of childhood ALL was found (OR=3.86, 95% CI=1.68 – 8.86); yet among girls, the risk was null

(OR=1.08, 95% CI=0.51 - 2.29). When divided into type of pain medication used, only epidural use (OR=1.67, 95% CI=1.00 – 2.77) was significantly associated with an increase in childhood ALL risk. However, a non-significant increase in risk was found among women who had been exposed to a gas mask (OR=4.00, 95% CI= 0.45 - 35.79), general anaesthetic (OR=1.57, 95% CI=0.61 – 4.05), and other pain medication (mainly local anaesthetic) (OR=1.38, 95% CI=0.72 – 2.62), while a slight decrease in risk was noted for analgesic injections (OR=0.79, 95% CI=0.46 - 1.37).

Multivariate Conditional Logistic Regression

Multivariate models were then built for each main exposure variable. When controlling for confounding, overall use of at least one medication during pregnancy (see Table 6a) did not significantly increase childhood ALL risk in our data set. Use of at least one type of medication versus none was associated with a small increase in childhood ALL risk (OR=1.15, 95% CI=0.66 – 1.99), while a slight protective effect was seen among women who used only one type of medication was used versus none (OR=0.90, 95% CI=0.50 - 1.61). However, a moderate increase in childhood ALL risk was found in the offspring of mothers who reported using two or more different types of medication versus none (OR=1.86, 95% CI=0.74 – 4.65).

The results of the models for the individual types of medications used during pregnancy are also shown in Table 6a. None of the medications were significantly associated with childhood ALL risk yet they all showed at least a slight increase in risk. Risk associated with use of anti-nausea medication (OR=1.02, 95% CI= 0.18 – 5.92) and antibiotics (OR=1.35, 95% CI= 0.48 - 3.82) were close to null, yet the point estimate increase in risk associated with use of analgesics

(OR=2.12, 95% CI=0.37 – 12.09) and illicit drugs (OR=2.44, 95% CI=0.66 – 9.00) were more than two-fold.

The confounding variables that were controlled for in the above models are shown in the footnote of each table. Interaction between the exposure variable and child's sex, age at diagnosis, and mother's age at birth was not found to be significant in any of the models.

Risk of childhood ALL in the offspring of mothers who were exposed to pain medication during delivery was modelled next (see Table 6b). Children of mothers who were exposed to pain medication during delivery were nearly twice as likely to develop ALL compared to children of mothers who were not exposed (OR=1.88, 95% CI=1.05 - 3.31). Again, significant interaction with child's sex was found; childhood ALL risk was three and a half fold higher among exposed male children versus non-exposed males (OR=3.61, 95% CI=1.51 – 8.61), while the risk for exposed versus non-exposed females was null (OR=0.96, 95% CI=0.40 – 2.28).

Discussion

Medication use during pregnancy

Percent use of medication during pregnancy in our study was slightly lower than the majority of published reports. On average, studies show that close to half of all women use medication during pregnancy. However, there are variations between studies with some countries reporting relatively higher overall usage (e.g., US, Italy) and others showing values closer to our own

findings (e.g., England). As well, many of these studies were conducted in a previous decade when use of medication during pregnancy was more prevalent.

Though case mothers consumed a higher overall dose of medication in our study, the number of different types of medications consumed was similar between cases and controls. The null result found for overall use of medication was consistent with previous studies on childhood cancer in general (106), leukaemia (107), and brain tumours in particular (116). Other researchers have reported an increased risk of leukaemia, both significant (40) and non-significant (104;105), associated with overall drug intake during pregnancy, however, the increased risk is typically neither large (OR<1.5) nor highly significant. Thus, our null result for overall use of medication during pregnancy is consistent with previous research.

The slight decrease in childhood ALL risk associated with maternal use of only one type of medication versus none has not been previously reported, nor has the increased risk among women who consumed two or more different types of medications during pregnancy. The increase in risk corresponding to the increase in number of types of drugs consumed may be an indication of a dose-response relationship, though actual dose taken was not employed in the calculation. The increased risk may also be a demonstration of either a threshold effect, or the result of combining different pharmaceuticals, or both. However, even though the point estimates suggest an increase in risk with increasing dose, the confidence intervals are wide and do overlap; thus, no firm conclusions can be revealed at this point. When the study is complete and

data from 1994-1999 are merged with data from 1980-1993, this finding may be clarified. However, neither study includes an exact measure of dose of medication used.

Among individual types of medications consumed, most investigators have not found an increase in childhood cancer risk associated with the use of antibiotics during pregnancy; including ALL (40;45;46;110), ANLL (53;105), retinoblastoma (93), or rhabdomyosarcoma (92). Others, however, have reported an increased risk of childhood cancer death (106) and childhood leukaemia (17;108) associated with antibiotic use during pregnancy. Similar to the latter studies, a moderate, yet non-significant, increase in childhood ALL risk was found in our study. However, without a larger study or more exposed subjects a definitive conclusion cannot be made.

Previous studies on use of anti-nausea medication during pregnancy and childhood cancer risk show mixed results. Maternal use of anti-nausea medication was not found to increase the risk of brain tumours (54;122) or neuroblastoma (118) in the offspring. However, use was reported to be associated with an increased risk of astrocytoma (97), retinoblastoma (93), Wilms' tumour (114), and leukaemia (49). Moreover, Robison (53) found an increased risk of ANLL and a dose-response relation in the offspring of mothers who used anti-nausea medication while pregnant. Though, in our study, a larger number of cases than controls did use anti-nausea medication during pregnancy, once confounding variables were included in the model the association was reduced to unity. Thus, based on our findings and the mixed results from previous reports, anti-nausea medication during pregnancy does not seem to be a strong risk factor for childhood ALL.

However, without a larger number of exposed subjects allowing for a stable risk estimate, conclusive statements cannot be made.

Most previous studies have not found a significantly increased risk of leukaemia (46;52), brain tumours (116), rhabdomyosarcoma (92), or Wilms' tumour (114;124) related to use of analgesics during pregnancy. However, Schwartzbaum, et al. (113) did find a significant increase in risk of neuroblastoma in the offspring of mothers who used pain relievers during pregnancy. Though the point estimate in our study was just above two, the risk estimate is highly unstable and the confidence interval includes unity. Thus, a null effect associated with analgesic use during pregnancy is likely the most accurate interpretation of our data.

On the other hand, neurally active drugs including barbiturates, narcotic analgesics, hypnotics, tranquillisers, and sedatives or sleeping pills are almost always associated with an increased risk of leukaemia (40;46;52;53;117), brain tumours (54), neuroblastoma (113;118), and rhabdomyosarcoma (92). Though some investigators have found no relation between neurally active drugs and brain tumours (116;119;120). In our study, no subjects reported consuming prescription analgesics during pregnancy, while sleeping pills and tranquillisers were taken by only one case mother each. It may be that only strong pain relievers, or ones that relieve pain/discomfort through different bio-chemical pathways than regular analgesics, increase childhood ALL risk. However, it was not possible to estimate such a risk in our study.

Most studies which have examined maternal use of illicit drugs during pregnancy and risk of childhood cancer have found a positive relation with various cancers, including leukaemia (53), brain tumours (97), and rhabdomyosarcoma (92). However, Bunin, et al. (93) found no increase in risk of retinoblastoma associated with use of recreational drugs during pregnancy. In our study only one subject reported using illicit drugs during pregnancy, however, we did find a moderate though non-significant increase in childhood ALL risk among the offspring of mothers who allegedly used illicit drugs in the year prior to birth. The larger study will be necessary to confirm this association, yet the increase in risk cannot be overlooked. Moreover, the consequences of finding a significant increase in risk associated with illicit drug use could be immense, especially since the risk period is not limited to pregnancy.

Thus, for individual medications, the number of exposed subjects is generally too small for any stable and/or significant results to be seen. An increase in childhood ALL risk associated with use of antibiotics, anti-nauseas, or analgesics during pregnancy is not suspected. However, the positive association between use of illegal drugs and childhood ALL risk should not be discounted. There is a biologic basis for such an effect as well as consistent findings with previous research. Though the increase in risk among mothers who used illicit drugs in the year prior to birth is nearly two and a half times the risk of non-users, the point estimate is not statistically significant and could be due chance or confounding by a factor that was not measured or controlled for. Again, without a larger study, conclusive statements cannot be made.

The findings for overall use of different types of medications are intriguing, but could also be strengthened through the larger study. If a true threshold does exist, below which mothers can safely consume medication, and above which risk increases significantly, the public health impact could be enormous. Moreover, the slight decrease in risk associated with minimal use of medication may be an indication of a minor maternal infection that could potentially reduce childhood ALL risk by strengthening the infant's immune system. The decreased childhood ALL risk among lower SES families could support this theory.

Pain medication during delivery

Unlike medication use during pregnancy, medication used to control pain during delivery was associated with a significant increase in risk of childhood ALL in our study, even after controlling for numerous confounding variables. Similar results were reported by other investigators for all childhood cancers combined (87), as well as leukaemia (37;46;106), lymphoma (123), Wilms' tumour (124), and brain tumours (116;125;126). Moreover, significant interaction was found with child's sex, where risk was increased for male offspring only, which was found by at least one other investigator (37). Still, other studies have shown no association between pain medication use during delivery and risk of childhood cancer in general (128), leukaemia (35;52;110), brain tumours (54;122;126), or retinoblastoma (93). In fact, general anaesthesia used during labour was found to be slightly protective for childhood astrocytoma by one investigator (97).

When broken down by type of pain medication used all types, except analgesics, showed a positive relation with childhood ALL risk. However, only risk associated with use of epidurals was significant, and the confidence interval still included one. It may be that the number of exposed subjects in the individual categories of pain relievers is too small to discern true increases in risk versus null or protective effects; and only after the numbers are compiled are they large enough to see stable, significant results. However, the biologic mechanisms by which use of pain medication during delivery could increase the child's risk of ALL are not obvious. For instance, the strongest association found was for epidurals, yet this type of medication is the least likely to affect the neo-nate.

Though the significant increase in risk associated with pain medication used during delivery should not be discounted, it is unlikely to be a direct causal agent. Use of pain medication during delivery may be a marker for another, unmeasured and/or uncontrolled for exposure. Perhaps only children who are also exposed to another, albeit common, risk factor are at an increased risk due to a synergistic or two-hit effect. Alternatively, the overall finding of an increased risk may be due to recall bias or chance. Given the mixed results from previous studies, a definitive conclusion cannot be made at this point. However, there is enough evidence to warrant further investigation of this effect.

Study Strengths and Limitations

It is unlikely that recall bias contributed to the elevated risk estimates found in this study. Not all exposures that would likely be considered "bad" or dangerous were elevated among case

mothers. For instance, both alcohol and tobacco usage during pregnancy were more commonly reported by control mothers, and some controls reported using certain medications more often or at higher doses than cases. If anything, the extent of time between pregnancy and questionnaire completion may have attenuated the results due to non-differential misclassification. Still, the actual extent of bias cannot be known without a validation study.

As well, selection bias is unlikely to have occurred or affected the results of this study. Recruitment of both case and control subjects was province-wide and, hence, from the same study base. Moreover, the response rate for both groups was extremely high. Thus, selection of subjects for this study was in essence independent of exposure status, virtually eliminating the possibility of selection bias affecting the results.

To reduce the possibility of information bias, in addition to recall bias, and provide more accurate risk estimates for both case and control subjects, objective, valid exposure measurements need to be developed and employed. As well, route and dose of exposure could affect the offspring's ALL risk and should be accounted for in the analysis. In fact, the biologic mechanisms that could explain the observed increases in risk need to be better understood. It seems likely that most cancers occur as a result of the interaction between environmental exposures and genetic make-up. Therefore, exposure measurements should be combined with molecular biology as subgroups of children may be more susceptible due to mutated genes or genes that are not expressed (i.e., null alleles).

As previously mentioned, the elevated risk of developing ALL associated with some of the factors examined in this study may be due to chance. The possibility of chance findings is evident in all epidemiologic studies, but the potential was increased in our study due to the employment of multiple comparisons. However, given the strength and consistency of the increased ALL risk associated with use of pain medication during pregnancy, it is unlikely that this finding was due to chance. The fluctuating and weaker findings for overall use of medication and illicit drug use may have been more susceptible to chance.

Since it is impossible to gather information on every potential risk factor for childhood ALL, the reported increased risks seen may be due to the lack of control of an extraneous factor, including those encountered during early infancy or childhood. This lack of control could explain the significantly increased risk associated with pain medication during delivery as well as the slight increase in risk seen among mothers who used illicit drugs and/or two or more types of medication during pregnancy. This potential cannot be dismissed without further exploration into the studied factors.

Finally, confounding by indication cannot be ruled out as an explanation for the increased relative risks seen in this study. Maternal illness, or another factor which preceded and possibly determined the use of medication during pregnancy or delivery may itself be responsible for the increased ALL risk. Unfortunately, this type of confounding cannot be controlled without the use of a clinical trial and random assignment to specific medications (147).

Though some of the findings in this study are intriguing and possibly revealing, the larger study including more subjects and measured exposures is needed to confirm or reject the findings presented. As discussed in the section on sample size, the study's power to detect small increases in risk especially for individual medications was too low. Thus, to narrow the confidence intervals and achieve more confident and stable results the study combining cases from 1980 to 1999 will be necessary.

Conclusion

In conclusion it seems that overall use of medication during pregnancy is not a strong risk factor for the development of ALL in the offspring. In fact, a slight decrease in risk was seen among mothers who used only one type of medication versus none. However, risk of ALL in the offspring of mothers who used two or more types of medication while pregnant was nearly twice that of mothers who reported using no medications. Still, the finding was not statistically significant and a larger study is needed to narrow the confidence intervals and provide a more accurate estimate of relative risk.

The only individual "medication" in our study which showed the potential to be an independent risk factor for the development of childhood ALL is the use of illicit drugs in the year prior to pregnancy. Although risk of childhood ALL among illicit drug users was nearly two and a half times the risk of non-drug users, the finding was not statistically significant. Thus, it is possible that the increased risk may be the result of other leukemogenic exposures common among illicit drug users rather than a direct, causal effect. This effect should be investigated further for a more

definitive conclusion. Though some of the point estimates for the other medications examined in this study were above one, none came close to significance. Again, a larger study should be done to confirm these results, but conflicting findings are unlikely.

Use of pain medication during delivery, on the other hand, appeared to be a strong and independent risk factor for the development of childhood ALL in our study. Risk remained elevated and significant even after numerous potential confounding variables were considered. The significant interaction with child's sex makes the result even more intriguing, especially given the similar findings by Zack et al. However, as previously stated, the biologic mechanisms are not clear and the increased risk could be due to another uncontrolled for factor. Nevertheless, this relationship should be explored further.

Although use of medication during pregnancy does not seem to greatly affect the offspring's risk of developing ALL, it can increase the child's risk of other medical problems and should continue to be monitored closely. Furthermore, although the majority of patients now survive childhood ALL, research into its' aetiology should proceed as hundreds of Canadian children and their families still suffer through the treatment and its aftermath each year.

Tables and Appendices

Appendix 1: Established and Suspected Risk Factors of Childhood ALL

Established Risk Factors	*Suspected Risk Factors*
Genetic syndromes and abnormalities	High socioeconomic status
eg., Down's syndrome	High birth weight
Ataxia Telangiectasia	Maternal age at delivery
Kleinfelters syndrome	Fertility problems and history of fetal loss
Ionizing radiation (*in utero*)	Hormones (including nausea)
	Electromagnetic fields
	Occupational exposures
	Tobacco and alcohol use during pregnancy
	Recreational drug use during pregnancy
	Medication use during pregnancy
	Delivery factors
	eg., nitrous oxide
	anesthetics

Appendix 2: Variables included in risk factor questionnaire

1. Occupational exposures - mother and father

2. Reproductive history
   i. Miscarriages
   ii. # of pregnancies

3. Conception and birth control
   i. medication to help pregnancy
   ii. use of OC's and other birth control

4. Gestational history for index child
   i. eclampsia
   ii. other problems
   iii. medication during pregnancy
   iv. problems during pregnancy
   v. x-rays
   vi. bone fractures
   vii. hot objects

5. Birth of index child
   i. simple or difficult birth
   ii. use of oxygen or fluorescent lights
   iii. medications
   iv. epidural

6. Mother and child's use of heating products
   i. x-rays
   ii. electric blankets, etc
   iii. fractures
   iv. CTs, nuclear medicine
   v. dental

7. Child's medication use
   i. thyroid
   ii. hormones
   iii. immunosuppressors
   iv. anti-inflammatories
   v. anti-epileptic

1.

8. Mother's medication use
   i. anti-nausea
   ii. sleeping pills
   iii. tranquilizers
   iv. diet pills
   v. vitamins
   vi. anti-epileptic
   vii. antibiotics
   viii. diabetes
   ix. fertility
   x. thyroid hormones
   xi. immunosuppressors, or steroids
   xii. anti-inflamatories
   xiii. pain killers
   xiv. anti-asthmatics
   xv. antacids
   xvi. illicit drug use

9. Father's medication use

10. Mother's smoking and alcohol practices
    i. smoking and ETS exposure
    ii. alcohol usage

11. Father's smoking and alcohol practices

12. Maternal and child residence history
    i. type of dwelling
    ii. heat and water source

13. Pesticide use
    i. insecticides, pets
    ii. bug spray - extermination
    iii. other products - herbicides, plant stuff, bug-off

14. Solvent exposure
    i. solvents, petrol
    ii. paints

15. Mother's medical history
    i. lupus
    ii. diabetes
    iii. asthma
    iv. epilepsy
    v. benign tumour
    vi. cancer/leukemia
    vii. ulcers
    viii. anaemia
    ix. rheumatoid arthritis
    x. immunodeficiency
    xi. thyroid
    xii. infectious recurrences
    xiii. mono
    xiv. congenital anomalies
    xv. renal, veins
    xvi. Chron's

16. Father's medical history

17. Ethnic background

18. Day care

Appendix 3: Participating Centres

1. Montreal Children's Hospital
2. Centre hospitalier de l'Université Laval
3. Centre hospitalier de l'Université de Sherbrooke
4. Hôpital Ste-Justine

Table 1a: Required sample size for use of medication

Number of subjects required to detect a relative risk of 1.8-2.0, assuming the background exposure is 0.40-0.50 (α=0.05, two-sided, β=0.20):

Background Exposure / Detectable Risk	***0.40***	***0.45***	***0.50***
RR = 1.8	184	183	187
RR = 1.9	154	154	158
RR = 2.0	132	133	136

Table 1b: Required sample size for use of individual medications

Number of subjects required to detect a relative risk of 2.5-3.5, assuming the background exposure is 0.05-0.15 (α=0.05, two-sided, β=0.20):

Background Exposure / Detectable Risk	***0.05***	***0.10***	***0.15***
RR = 2.5	271	151	112
RR = 3.0	176	99	75
RR = 3.5	129	73	56

Table 2: Response rates by year of diagnosis

Year of Diagnosis/ Subject Outcome	*1994*		*1995*		*1996*		*1997*	
	Cases	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
Total Eligible	45	47	50	45	46	51	44	33
Refusals	1	2	7	0	4	5	10	0
Lost to follow-up	0	1	0	2	0	4	0	1
No matching subject	0	0	3	4	1	0	0	0
Total Interviewed	44	44	40	39	41	42	32	32
Response Rate (Interviewed/Eligible)	**98%**	**94%**	**80%**	**87%**	**89%**	**82%**	**73%**	**97%**

Table 3: Distribution of Potential Confounders

Variable		*Number of Cases (N=157)*	*Number of Controls (N=157)*
Sex:	Male	94 (59.9%)	94 (59.9%)
	Female	63 (40.1%)	63 (40.1%)
Age of child at diagnosis:			
	<2 year	14 (8.9%)	14 (8.9%)
	2-5 years	98 (62.4%)	98 (62.4%)
	6-9 years	23 (14.6%)	23 (14.6%)
	10-14 years	22 (14.0%)	22 (14.0%)
Age of mother at delivery:			
	< 21 years	10 (6.4%)	13 (8.3%)
	21-25 years	41 (26.1%)	42 (26.8%)
	26-30 years	60 (38.2%)	69 (43.9%)
	31-35 years	34 (21.7%)	28 (17.8%)
	>35 years	12 (7.6%)	5 (3.2%)
Birth weight of index child:			
	<=3000 grams	31 (19.7%)	44 (28.0%)
	3001-3500 grams	69 (43.9%)	45 (28.7%)
	3501-4000 grams	40 (25.5%)	55 (35.0%)
	>=4001 grams	17 (10.8%)	13 (8.3%)
Household income at delivery:			
	< $20,000	29 (18.6%)	23 (14.7%)
	$20-29,000	37 (23.7%)	36 (23.1%)
	$30-39,000	28 (18.0%)	31 (19.9%)
	$40-49,000	24 (15.4%)	31 (19.9%)
	=>$50,000	38 (24.4%)	35 (22.4%)
Mother's level of education:			
	finished primary school (Gr.10)	28 (17.8%)	32 (20.4%)
	finished secondary school (Gr. 11)	49 (31.2%)	56 (35.7%)
	finished college (Gr. 12-13)	40 (25.5%)	37 (23.6%)
	finished university	40 (25.5%)	32 (20.4%)
Smoking during pregnancy:			
	Yes	52 (33.1%)	58 (36.9%)
	No	105 (66.9%)	99 (63.1%)
Dose of smoking during pregnancy:			
	None	105 (66.9%)	99 (63.1%)
	1-14 cig/day	33 (21.0%)	34 (21.7%)
	15-24 cig/day	13 (8.3%)	15 (9.6%)
	25 + cig/day	6 (3.8%)	9 (5.7%)
Drinking during pregnancy:			
	Yes	51 (32.5%)	58 (36.9%)
	No	106 (67.5%)	99 (63.1%)

Dose of drinking during pregnancy:		
no drinks/month	106 (67.5%)	99 (63.1%)
1-2 drinks/month	15 (9.6%)	26 (16.6%)
3-8 drinks/month	16 (10.2%)	16 (10.2%)
> 8 drinks/month	20 (12.7%)	12 (10.2%)
X-ray during pregnancy:		
Yes	14 (9.0%)	11 (7.0%)
No	142 (91.0%)	146 (93.0%)
Abdominal x-ray during pregnancy:		
Yes	4 (2.6%)	5 (3.2%)
No	153 (97.4%)	152 (96.8%)
Type of delivery:		
Vaginal birth	133 (85.8%)	142 (90.4%)
Cesarean	22 (14.2%)	15 (9.6%)
Congenital Abnormalities:		
Yes	49 (31.2%)	46 (29.3%)
No	108 (68.8%)	111 (70.7%)
One congenital abnormality:		
Yes	41 (26.1%)	33 (21.0%)
No	116 (73.9%)	124 (79.0%)
Two or more abnormalities:		
Yes	8 (5.1%)	13 (8.3%)
No	149 (94.9%)	144 (91.7%)
Illness during pregnancy:		
Yes	89 (56.7%)	73 (46.5%)
No	68 (43.3%)	84 (53.5%)
One illness only:		
Yes	51 (32.5%)	41 (26.1%)
No	106 (67.5%)	116 (73.9%)
Two or more illnesses:		
Yes	38 (24.2%)	32 (20.4%)
No	119 (75.8%)	125 (79.6%)
Weeks of nausea during pregnancy		
None	56 (35.7%)	78 (49.7%)
<13 weeks	69 (44.0%)	59 (37.6%)
13-25 weeks	18 (11.5%)	12 (7.6%)
>25 weeks	14 (8.9%)	8 (5.1%)

Table 4a: Use of Medication During Pregnancy

Variable		*Number of Cases (N=157)*	*Number of Controls (N=157)*
Overall use of medication during pregnancy: (excluding vitamins)	Yes	50 (32.9%)	43 (27.4%)
	No	107 (68.2%)	114 (72.6%)
Number of different types of medication used:			
	1 type	34 (21.7%)	34 (21.7%)
	2 types	13 (8.3%)	8 (5.1%)
	3 types	2 (1.3%)	1 (0.6%)
	4 types	1 (0.6%)	0 (0.0%)
Categories of Medication:			
Oral contraceptives		2 (1.3%)	2 (1.3%)
Anti-nauseas		**6 (3.8%)**	**2 (1.3%)**
Sleeping pills		1 (0.6%)	0 (0.0%)
Tranquilizers		1 (0.6%)	0 (0.0%)
Diet pills		0 (0.0%)	0 (0.0%)
Epileptic medication		2 (1.3%)	0 (0.0%)
Antibiotics		**14 (8.9%)**	**8 (5.1%)**
Fertility hormones		0 (0.0%)	2 (1.3%)
Diabetes medication		2 (1.3%)	3 (1.9%)
Thyroid medication		1 (0.6%)	3 (1.9%)
Immunosuppressant or steroid		2 (1.3%)	2 (1.3%)
Anti-inflammatory		0 (0.0%)	0 (0.0%)
Analgesic OTC (tylenol, aspirin)		**5 (3.2%)**	**2 (1.3%)**
Analgesic - prescription		0 (0.0%)	0 (0.0%)
Antihistamines		3 (1.9%)	1 (0.6%)
Anti-asthmatics		5 (3.2%)	3 (1.9%)
Antacid		9 (5.7%)	12 (7.6%)
Other medication (monistat, iron, calcium)		15 (9.6%)	11 (7.0%)
Illicit drugs		1 (0.6%)	0 (0.0%)
Illicit drugs in year prior to birth		**9 (5.7%)**	**4 (2.6%)**
Vitamins		**119 (75.8%)**	**127 (80.9%)**

Table 4b: Average dose of medication used during pregnancy

Category of Medication	*Average number of pills taken by cases (N=157) (SD)*	*Average number of pills taken by controls (N=157) (SD)*
Total medication (excluding vitamins)	**82.8 (228.1)**	**61.0 (160.2)**
Categories of Medication:		
Oral contraceptives	3.9 (34.8)	3.6 (31.5)
Anti-nauseas	**7.4 (50.4)**	**5.6 (62.9)**
Sleeping pills	0.1 (1.2)	0.0
Tranquilizers	0.7 (8.4)	0.0
Diet pills	0.0	0.0
Epileptic medication	10.7 (99.7)	0.0
Antibiotics	**3.4 (18.6)**	**2.0 (11.1)**
Fertility hormones	0.0	4.3 (47.4)
Diabetes medication	8.9 (78.8)	2.5 (19.7)
Thyroid medication	1.8 (22.3)	5.4 (38.5)
Immunosuppressant or steroid	1.0 (9.9)	1.8 (22.3)
Anti-inflammatory	0.0	0.0
Analgesic OTC (tylenol, aspirin)	**7.9 (72.1)**	**2.1 (22.6)**
Analgesic - prescription	0.0	0.0
Antihistamines	1.1 (11.3)	3.6 (44.7)
Anti-asthmatics	7.4 (53.7)	4.3 (45.1)
Antacid	13.1 (70.9)	17.2 (84.6)
Other medication (monistat, iron, calcium)	14.8 (65.0)	7.5 (50.7)
Illicit drugs	0.5 (6.4)	0.0
Illicit drugs in year prior to birth	**10.6 (90.1)**	**5.4 (50.0)**
Vitamins	**144.9 (114.6)**	**151.9 (94.6)**

Table 5a:Univariate Conditional Logistic Regression - Medication use during pregnancy

Variable in conditional logistic regression model	*No. of exposed Cases/Controls*	*Odds Ratio*	*95% CI*
Used at least one medication during pregnancy (vs. none)	**50/43**	**1.26**	**0.76 – 2.09**
Used only one type of medication during pregnancy (vs. none)	34/34	1.00	0.58 - 1.72
Used two or more types of medication during pregnancy (vs. none)	16/9	1.88	0.80 - 4.42
Specific medications used during pregnancy:			
Anti-nausea medication	6/2	3.00	0.61-14.86
Antibiotics	14/8	2.00	0.75 – 5.33
Analgesics	5/2	2.50	0.49 – 12.87
Illicit drugs in year before pregnancy til birth	9/4	2.25	0.69 – 7.31

Table 5b: Univariate Conditional Logistic Regression - Pain medication use during delivery

Variable in conditional logistic regression model	*No. of Exposed Cases/Controls*	*Odds Ratio*	*95% CI*
Used pain medication during delivery	**100/80**	**2.05**	**1.20 - 3.50**
Male subjects only	61/42	3.86	1.68 - 8.86
Female subjects only	39/38	1.08	0.51 - 2.29
Specific pain medications during delivery:			
Anti-pain or analgesic injection	29/35	0.79	0.46 - 1.37
Gas mask	4/1	4.00	0.45 - 35.79
Epidural	54/38	1.67	1.00 - 2.77
General anesthetic	12/8	1.57	0.61 – 4.05
Other medication (mostly local anaesthesia to the perineum used with epidural)	27/21	1.38	0.72 – 2.62

Table 6a: Multivariate Conditional Logistic Regression - Use of medication during pregnancy

Main exposure variable in regression model	*Parameter Estimate*	*Standard Error*	*Odds Ratio*	*95% Confidence Interval*
Used at least one medication during pregnancy (vs. none)[1]	**0.14**	**0.28**	**1.15**	**0.66 - 1.99**
Use of only one type of medication (vs. none)[1]	-0.10	0.30	0.90	0.50 - 1.61
Use of two or more types of medication (vs. none)[1]	0.62	0.47	1.86	0.74 – 4.65
Specific medications used during pregnancy:				
Anti-nausea medication[2]	0.02	0.90	1.02	0.18 – 5.92
Antibiotics[3]	0.30	0.53	1.35	0.48 - 3.82
Analgesics[4]	0.75	0.89	2.12	0.37 – 12.09
Illicit drugs in year prior to birth[5]	0.89	0.67	2.44	0.66 - 9.00

1. adjusted for smoking and drinking during pregnancy, xray exposure in the year prior to birth, and congenital abnormalities
2. adjusted for smoking and drinking during pregnancy, illness during pregnancy, nausea during pregnancy, mother's education and household income at delivery, and xray exposure during pregnancy
3. adjusted for mother's education and household income at delivery, illness during pregnancy, xray exposure in year prior to birth, and congenital abnormalities
4. adjusted for smoking and drinking during pregnancy, illness during pregnancy, xray exposure in year prior to birth and mother's age at delivery
5. adjusted for smoking and drinking during pregnancy, mother's education and household income at delivery, and congenital abnormalities

Table 6b: Multivariate Conditional Logistic Regression - Pain medication during delivery

Main exposure variable in regression model	*Parameter Estimate*	*Standard Error*	*Odds Ratio*	*95% Confidence Interval*
Pain medication during delivery[1]	**0.62**	**0.29**	**1.88**	**1.05 – 3.31**
Male children only[1]	1.23	0.44	3.43	1.45 – 8.10
Female children only[1]	-0.05	0.44	0.96	0.40 – 2.28

1. adjusted for mother's education and household income at delivery, and birth weight

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