Nicotine Replacement Therapy in Pregnancy and Major Congenital Anomalies in Offspring

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abstract

BACKGROUND AND OBJECTIVES: Nicotine replacement therapy (NRT) is now being used as a smoking cessation aid during pregnancy, although little is known about fetal safety. We assessed the relationship between early pregnancy exposure to NRT or smoking with major congenital anomalies (MCA) in offspring.

METHODS: We studied 192 498 children born in the United Kingdom between 2001 and 2012 with linked mother–child primary care records. The absolute risks of MCAs in the NRT group (women prescribed NRT during the first trimester or 1 month before conception [and therefore likely consumed during the first trimester]) and odds ratios (ORs) and 99% confidence intervals (CIs) were compared with those of women who smoked during pregnancy and with a control group (women who neither smoked nor were prescribed NRT); logistic regression models adjusted for maternal morbidities that increase MCA risk were used for analysis.

RESULTS: MCA prevalence was 288 per 10 000 live births (5535 children with ≥1 MCA). Maternal morbidities were most common in the NRT group (35%) followed by smokers (27%) and the control group (20%). Compared with the control group, adjusted ORs for MCAs in the NRT group and smokers were 1.12 (99% CI: 0.84–1.48) and 1.05 (99% CI: 0.89–1.23), respectively. The OR comparing the NRT group directly with smokers was 1.07 (99% CI: 0.78–1.47). There were no statistically significant associations between maternal NRT and system-specific anomalies except for respiratory anomalies (OR: 4.65 [99% CI: 1.76–12.25]; absolute risk difference: 3 per 1000 births), which was based on 10 exposed cases.

CONCLUSIONS: For most system-specific MCAs, we found no statistically significant increased risks associated with maternal NRT prescribed during pregnancy, except for respiratory anomalies. Although this study is the largest published to date, NRT use in pregnancy remains rare; thus, the statistical power was limited. Higher morbidities in those women prescribed NRT may also be an explanatory factor. Nevertheless, absolute MCA risks were similar between women who smoked and those prescribed NRT during pregnancy.

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WHAT'S KNOWN ON THIS SUBJECT: Smoking has been found to increase the risk of some specific congenital anomalies; however, results remain inconsistent. Nicotine replacement therapy (NRT) is increasingly being used as for smoking cessation in pregnancy although little is known about its association with congenital anomalies.

WHAT THIS STUDY ADDS: Being prescribed NRT while pregnant was not associated with major congenital anomalies (MCA), except a small increase in respiratory anomalies (3/1000 births). This must be considered in context of the rarity of MCAs and higher morbidities in the NRT group.

Maternal smoking during pregnancy is a well-established risk factor for many adverse perinatal outcomes.[1] The association with congenital anomalies (CAs) in offspring is less clear because studies have produced mixed results.[2–5] A large systematic review of observational studies reported no association (odds ratio [OR]: 1.01 [95% confidence interval (CI): 0.96–1.07]) for all anomalies, but individual meta-analyses for some system-specific anomalies (including heart defects, musculoskeletal defects, and orofacial clefts) revealed increased risks.[6]

Despite these findings, many women still smoke during pregnancy: 12% in the United Kingdom,[7] 13% in the United States,[8] and 15% in Australia.[9] Internationally, significant resources have been directed at reducing maternal smoking during pregnancy, including the provision of behavioral support and prescription of nicotine replacement therapy (NRT). In the United Kingdom, NRT became available via National Health Service (NHS) prescriptions in 2001 but was initially contraindicated during pregnancy. In 2005, the Medicines and Healthcare Products Regulatory Authority broadened the United Kingdom's NRT licensing arrangements to include pregnant women.[10] Approximately 11% of pregnant smokers in the United Kingdom are now prescribed NRT in primary care despite a paucity of evidence concerning the safety of this therapy in pregnancy.[11] The 2005 pregnancy licensing decision of the Medicines and Healthcare Products Regulatory Authority was based on the conclusion that NRT use was likely to be less harmful than smoking despite the inconclusive evidence regarding its general maternal or fetal safety.[10] Evidence of safety specifically in relation to CA risks is limited to 1 observational study of linked clinical data from Denmark, which did not find an increased risk with major CAs, and 2 randomized controlled trials of pregnant women in England and France, both of which found a reduced risk but were not adequately powered to assess this outcome.[12–14]

Using a large population-based pregnancy cohort, the present study investigated whether exposure to NRT increases the risk of major congenital anomalies (MCAs) compared with pregnant women who neither smoked nor were prescribed NRT antenatally and who smoked during pregnancy.

METHODS

Data Source and Study Population

The Health Improvement Network (THIN) is a UK database of anonymized electronic primary care records, with a high validity of recorded diagnoses and prescriptions.[15] THIN has been previously validated for its recorded population prevalence of smoking at national[16] and regional[17] levels, and fertility rates in THIN are highly comparable to national fertility rates.[18] At the time of the present study, THIN contained longitudinal, prospectively collected data from 570 general practices across the United Kingdom, and it covered 6% of the UK population.[19]

A pregnancy cohort was created by using general practice records from all women in THIN aged 15 to 49 years by linking pregnancy and birth-related codes in women's medical records to live births of children registered in the same household at the time of delivery. We included live births between January 2001 and December 2012. Only live births were examined because the process of detecting and recording findings of CAs for pregnancies ending in miscarriages or stillbirths is not comprehensive.

Major Congenital Anomalies

Information on children's MCA diagnoses recorded in THIN was extracted by using Read Codes[20] mapped to the European Surveillance of Congenital Anomalies (EUROCAT) classification system. This system identifies all conditions classified as MCAs coded according to the Q chapter of the *International Classification of Diseases, 10th Revision* (ICD-10),[21] and a small number of conditions in other ICD-10 chapters, and it categorizes them into system-specific subgroups.[22] Diagnoses recorded at any age during children's primary care registration in THIN (average length of registration data were up to 5 years of age) were included. This method exhibited good completeness of recording in a previous validation study comparing MCAs in THIN versus EUROCAT registry data, with 72% of diagnoses being recorded before the child's first birthday.[23] In line with EUROCAT, minor CAs (eg, lip hypertrophy, congenital flat foot) were excluded.[22] Using this method, the prevalence of specific MCAs in THIN is consistent with the prevalence from British registries contributing to EUROCAT.[23] Children with anomalies specifically attributed to known teratogens (eg, fetal alcohol syndrome, fetal valproate syndrome) were excluded from the study population.

Exposure Assessment

Prescriptions for NRT were extracted by using Multilex drug codes for all formulations available in the United Kingdom according to the British National Formulary.[24] All pregnant women with NRT prescribed according to their primary care records during the first trimester of pregnancy (ie, the most critical period for teratogenic effects to occur) or within 4 weeks before their estimated conception date were classified as the NRT group. Prescriptions in the 4 weeks before conception were included because it is likely that these products could be consumed during early stages of the first trimester. The recording of smoking status during pregnancy in primary care data is via prospective ascertainment made during women's antenatal clinical consultations with physicians, nurses, or midwives. This information was extracted by using smoking status

Read Codes, and each woman's smoking status was determined during the first trimester based on a previously validated algorithm.[16] Smoking status codes from only first trimester was used to categorize women as smokers (those recorded as smokers at any point from conception until the end of the first trimester but without NRT prescriptions as these were in the NRT group) or into a control group (those exclusively recorded as nonsmokers at any point from conception until the end of the first trimester). Electronic recording of smoking and smoking cessation advice are 2 of the pay-for-performance targets in the Quality and Outcomes Framework (QOF) that were introduced in the United Kingdom in 2004 as part of the primary care contract. Two QOF rules were used to further categorize women as nonsmokers (control subjects). First, according to the QOF requirements, general practitioners (GPs) are not required to record the smoking status of patients after the age of 25 years if they had never smoked until that age. Therefore, if there was no smoking status recorded during pregnancy, but women were recorded as having never smoked at any time during their active registration period when they were aged >25 years, they were included in the control group. This rule makes the assumption that women will not start smoking for the first time after 25 years of age (eg, a woman who is recorded as a never smoker at age 26 years will likely still be a nonsmoker during her pregnancy at 28 years). Second, if a patient who once smoked has been recorded as an ex-smoker for at least 3 years, QOF requirements are that GPs need no longer check and update patients' smoking status records. Based on this QOF rule, if a woman did not have a smoking status recorded during pregnancy but was recorded as an ex-smoker for 3 consecutive years before pregnancy, we categorized her as an ex-smoker, and she was thus included in the control group. This rule uses the assumption that after 3 years of abstinence, relapse to smoking is rare; this assumption has been reinforced in long-term follow-up studies.[25] After considering these QOF rules, all remaining women with missing smoking status were excluded from the study.

Other Maternal Covariates

Information on potential confounders such as women's age at conception, socioeconomic deprivation (Townsend deprivation index),[26] prepregnancy body mass index, and recorded diagnoses of medical conditions before or during pregnancy (hypertension, epilepsy, diabetes, asthma, and mental illness including depression, anxiety, bipolar disorder, schizophrenia, and other psychoses) was also extracted due to the associations of these conditions or their treatments with both CAs and maternal smoking.[7,27–37] All code lists are available from the authors on request.

Statistical Analysis

To estimate the disease burden of all major and each system-specific MCA group, absolute risks (per 10 000 live births) for the overall population and for each exposure group (ie, NRT group, smokers, control group) were calculated. ORs for any MCA and each system-specific anomaly group were calculated for the NRT group and smokers in relation to the control group by using logistic regression analysis. Some women in the study period had >1 pregnancy; potential correlation was accounted for by using generalized estimating equations with an exchangeable correction structure.[38] In recognition of the large number of exposure and outcome categories, 99% CIs were calculated for ORs. In accordance with 99% CIs, we considered a P value <.01 to indicate a statistically significant association; however, exact P values are also presented for transparent reader assessment of associations potentially arising by chance. To determine whether each of the potential confounders was associated with the exposure and with the outcome, χ^2 tests were used. Covariates with statistically significant associations at a 5% level of significance were included in the final multivariable model. A second analysis was conducted with the reference group changed to smokers, and ORs (99% CIs) for MCAs in the NRT group were recalculated.

Ethical approval for analysis of the THIN data was obtained from the NHS Medical Research Ethics Committee (REC Ref. 04/MRE01/9).

RESULTS

Baseline Characteristics

Of 192 498 live-born children, 5535 had at least 1 MCA (288 per 10 000 live births). The distribution of maternal age at conception, socioeconomic status, and preconception BMI was similar in women whose children had any MCA and women whose children did not have any MCA. The MCA group had a slightly higher proportion of maternal morbidities (Table 1).

Table 2 presents the characteristics of mothers according to each exposure group. Mothers in the smoking group were younger compared with the NRT group and the control group. About one-quarter of mothers in the NRT and smoking groups (22.8% and 25.3%, respectively) belonged to the most deprived group (Townsend quintile 5) compared with 10.1% in the control group. In addition, higher proportions of mothers in the NRT and smoking groups had maternal morbidities than in the control group (particularly mental illness and asthma), with slightly higher proportions in the NRT group compared with the smoking group. Overall, 35% of women in the NRT group had at least 1 diagnosed

TABLE 1 Maternal Characteristics of All Live-Born Children With and Without MCAs

Characteristic	All Children (N = 192 498)		Children Without MCAs (n = 186 963)		Children With MCAs (n = 5535)	
	n	%	n	%	n	%
Age at conception, y						
15–19	3515	1.8	3397	1.8	118	2.1
20–24	17 969	9.3	17 378	9.3	591	10.7
25–29	51 038	26.5	49 622	26.5	1416	25.6
30–34	70 000	36.4	68 055	36.4	1945	35.1
35–39	40 988	21.3	39 850	21.3	1138	20.6
40–44	8567	4.5	8266	4.4	301	5.4
45–49	421	0.2	395	0.2	26	0.5
Townsend deprivation index score						
Quintile 1 (least deprived)	49 610	25.8	48 192	25.8	1418	25.6
Quintile 2	38 439	20.0	37 343	20.0	1096	19.8
Quintile 3	37 412	19.4	36 353	19.4	1059	19.1
Quintile 4	31 665	16.4	30 700	16.4	965	17.4
Quintile 5 (most deprived)	21 227	11.0	20 600	11.0	627	11.3
Missing	14 145	7.3	13 775	7.4	370	6.7
Preconception BMI						
Normal (18.5–24.9)	62 795	32.6	61 011	32.6	1784	32.2
Underweight (<18.5)	3836	2.0	3719	2.0	117	2.1
Overweight (25–29.9)	30 888	16.0	29 991	16.0	897	16.2
Obese (≥30)	21 406	11.1	20 803	11.1	603	10.9
Missing	73 573	38.2	71 439	38.2	2134	38.6
Asthma	16 213	8.4	15 699	8.4	514	9.3
Hypertension	5838	3.0	5619	3.0	219	4.0
Diabetes	6088	3.2	5851	3.1	237	4.3
Mental illness	14 559	7.6	14 088	7.5	471	8.5
Epilepsy	812	0.4	782	0.4	30	0.5

morbidity compared with 27% of smokers and 20% of control subjects.

Absolute and Relative Risks of MCAs

The absolute risk of MCAs in the NRT group was slightly higher than in the control group (336 per 10 000 live births compared with 285 per 10 000 live births) (Table 3). Similar higher risks were seen for the most common anomalies in the NRT group (heart, limb, genital, and urinary defects) compared with the control groups. The absolute risks of MCAs in smokers were found to be similar to those in the NRT group (315 per 10 000 live births for any MCA).

The OR for MCAs in the NRT group compared with the control group was 1.12 (99% CI: 0.84–1.48]; P = .31) (Table 4). There was no statistically significant increased risk of MCAs in smokers compared with the control group (OR: 1.05 [99% CI: 0.89–1.23]; P = .47). The ORs for system-specific anomalies were broadly similar to the overall findings. The 99% CIs and associated P values showed no increased risk of any system-specific MCA in the NRT group or smokers. The only exception was for respiratory system anomalies; the risk for these anomalies was higher in the NRT group compared with the control group (OR: 4.65 [99% CI: 1.76–12.25]; $P < .001$). These measures were based on a very small number of exposed cases (n = 10) and an absolute difference of 3 MCAs per 1000 live births.

The relative risk of MCAs in the NRT group was not appreciably altered when the reference group was changed to smokers (OR: 1.07 [99% CI: 0.78–1.47]; P = .58) (Table 5). There was an increased risk of respiratory anomalies in the NRT group compared with smokers (OR: 3.49 [99% CI: 1.05–11.62]; P = .007). However, as described earlier, this finding was based on 10 NRT-exposed cases.

DISCUSSION

Principal Findings

The present study found that women with NRT exposure during early pregnancy, as recorded in primary care medical records, did not have an increased risk of overall MCAs in offspring compared with women who smoked during pregnancy but did not use NRT and compared with nonsmokers. Furthermore, there was no evidence of associations between being prescribed NRT and system-specific MCAs during early pregnancy except for a small increased risk of respiratory anomalies.

Strengths and Limitations

This study is the largest to date to investigate the association between NRT prescribing in pregnant women and MCAs in their offspring. The study included 2677 children with maternal exposure to NRT in early pregnancy, which, although underpowered to assess most system-specific anomalies, was still 10 times larger than the only previous population-based study on this subject.[12] Although CAs in the United Kingdom are diagnosed in secondary care, major diagnoses should be communicated to primary care, and the prevalence of MCAs in THIN has been shown to be highly comparable to the UK registries contributing to EUROCAT surveillance.[39] Furthermore, CA diagnoses according to clinical coding in electronic primary care data have been validated against physician-provided written clinical records reported directly from the general practice.[40,41] To capture as many cases as possible, our case definition included MCA diagnoses made from birth up to any age during the child's registration with THIN practices (average age: 5 years).

Our measurement of NRT exposure was based on recorded GP prescribing, which has provided a more objective measurement of drug prescribing and use during pregnancy than self-reports by

TABLE 2 Maternal Characteristics According to Smoking and NRT Exposure in Early Pregnancy

Characteristic	NRT Group (n = 2677)		Smokers (n = 9980)		Control Group (n = 179 841)	
	n	%	n	%	n	%
Age at conception, y						
15–19	174	6.5	1240	12.4	2101	1.2
20–24	630	23.5	2849	28.5	14 490	8.1
25–29	772	28.8	2632	26.4	47 634	26.5
30–34	644	24.1	2004	20.1%	67 352	37.5
35–39	370	13.8	1006	10.1	39 612	22.0
40–44	84	3.1	240	2.4	8243	4.6
45–49	3	0.1	9	0.1	409	0.2
Townsend deprivation index score						
Quintile 1 (most affluent)	243	9.1	1036	10.4	48 331	26.9
Quintile 2	367	13.7	1247	12.5	36 825	20.5
Quintile 3	564	21.1	1964	19.7	34 884	19.4
Quintile 4	711	26.6	2562	25.7	28 392	15.8
Quintile 5 (most deprived)	610	22.8	2527	25.3	18 090	10.1
Missing	182	6.8	644	6.5	13 319	7.4
Preconception BMI						
Normal (18.5–24.9)	780	29.1	2949	29.5	59 066	32.8
Underweight (<18.5)	86	3.2	326	3.3	3424	1.9
Overweight (25–29.9)	466	17.4	1515	15.2	28 907	16.1
Obese (≥30)	385	14.4	1230	12.3	19 791	11.0
Missing	960	35.9	3960	39.7	68 653	38.2
Asthma	389	14.5	1041	10.4	14 783	8.2
Hypertension	63	2.4	183	1.8	5592	3.1
Diabetes	91	3.4	215	2.2	5782	3.2
Mental illness	555	20.7	1525	15.3	12 479	6.9
Epilepsy	11	0.4	68	0.7	733	0.4

mothers in other studies.[12,42] In the United Kingdom, pregnant women can access NRT in settings other than the GP practice, such as through the stop smoking services for pregnancy (SSSP) of the NHS, as well as over-the-counter or off-the-shelf purchases in pharmacies. However, only 3% of pregnant women access an SSSP on average each year,[43,44] and a survey of all SSSPs in England conducted between April 2010 and March 2011 reported that almost one-half of the NRT provided by these services was issued through GPs.[45] Self-purchase of NRT is expected to be infrequent for several reasons: the prevalence of medication use without health professional consultation is lower during pregnancy than when women are not pregnant[46]; NRT packaging clearly instructs pregnant women to consult a physician before using these products; and women in the United Kingdom are entitled to free NHS prescriptions during pregnancy,[47] increasing the likelihood that women will obtain free NRT prescriptions through GPs rather than paying for them. Therefore, we believe that primary care data are a reliable source for measuring NRT exposure in pregnant women and that misclassification in the exposure measurement would be minimal.

TABLE 3 Absolute Risks of MCAs According to NRT Exposure and Maternal Smoking During Early Pregnancy

Variable	All Children (N = 192 498)		NRT Group (n = 2677)		Smokers (n = 9980)		Control Group (n = 179 841)	
	n[a]	n/10 000	n	n/10 000	n	n/10 000	n	n/10 000
All MCAs combined	5355	288	90	336	314	315	5131	285
Heart	1782	93	26	97	104	104	1652	92
Limb	1071	56	15	56	60	60	996	55
Genital system	914	47	16	60	51	51	847	47
Urinary system	511	27	12	45	20	19	479	27
Chromosomal	400	21	4	15	13	13	383	21
Musculoskeletal	380	20	10	37	28	28	342	19
Orofacial cleft	275	14	3	11	20	19	252	14
Digestive system	285	15	6	22	18	18	261	15
Nervous system	295	15	4	15	18	17	273	15
Other malformations[b]	280	15	5	19	18	18	257	14
Eye	226	12	3	11	15	14	208	12
Respiratory system	157	8	10	37	10	10	137	8
Genetic	162	8	0	—	9	9	153	9
Abdominal wall	32	2	0	—	3	2	29	2
Ear, face, and neck	38	2	0	—	3	2	35	2

—, indicates no cases.

[a] The total number may vary because each case may have >1 system anomaly.

[b] Including asplenia and conjoined twins.

In 2010, the Medicines and Health Regulatory Authority included harm reduction as an indication for NRT in smokers in the United Kingdom, which meant that smokers could use NRT to reduce their smoking. However, this indication only applies to smokers in the general population and not to pregnant women, for whom NRT is only indicated for smoking cessation. Therefore, we believe that simultaneous use of NRT and cigarettes should be minimal. Measuring this factor in an epidemiologic study would only be possible with a detailed follow-up study that would need to have multiple prospective recordings of women's smoking behavior. However, such a study has not been conducted to date, mainly because such studies to assess CA risks would be prohibitively large. Furthermore, measuring actual drug consumption in any large population-based study is pragmatically difficult (and is also a limitation of previous studies).[12]

Ascertaining accurate smoking status is also difficult, especially in pregnant women, because there is

TABLE 4 Adjusted ORs for MCAs in Children According to Maternal NRT Exposure and Smoking During Early Pregnancy, Using Only Gestational Smoking Status

Variable	NRT Group (n = 2677)		Smokers (n = 9980)	
	Adjusted OR[a,b] (99% CI)	P	Adjusted OR[a,b] (99% CI)	P
All MCAs combined	1.12 (0.84–1.48)	.31	1.05 (0.89–1.23)	.47
Heart	1.01 (0.60–1.70)	.96	1.09 (0.83–1.46)	.39
Limb	0.99 (0.50–1.95)	.98	1.04 (0.73–1.48)	.76
Genital system	1.14 (0.59–2.20)	.62	0.94 (0.63–1.38)	.66
Urinary system	1.82 (0.85–3.89)	.04	0.86 (0.47–1.57)	.51
Chromosomal	0.74 (0.19–2.78)	.56	0.71 (0.33–1.49)	.24
Musculoskeletal	1.79 (0.76–4.20)	.08	1.32 (0.76–2.29)	.19
Orofacial cleft	0.75 (0.17–3.40)	.63	1.40 (0.76–2.59)	.16
Digestive system	1.52 (0.51–4.51)	.32	1.30 (0.66–2.54)	.32
Nervous system	0.83 (0.22–3.09)	.72	1.01 (0.51–2.03)	.96
Other malformations[c]	1.16 (0.36–3.79)	.74	1.08 (0.55–2.11)	.76
Eye	0.89 (0.19–4.06)	.85	1.19 (0.58–2.46)	.52
Respiratory system	4.65 (1.76–12.25)	<.001	1.34 (0.54–3.31)	.41
Genetic	—	—	1.02 (0.37–2.81)	.96
Abdominal wall	—	—	0.77 (0.15–3.96)	.68
Ear, face, and neck	—	—	1.51 (0.34–6.64)	.48

—, no cases in the NRT group therefore no ORs presented.

[a] Reference category = control group.

[b] Adjusted for maternal age at conception, Townsend deprivation index score, maternal diabetes, asthma, mental illnesses, and multiple births.

[c] Including asplenia and conjoined twins.

a high potential for misreporting due to the social stigma attached to smoking in pregnancy. However, all previous studies investigating the association between maternal smoking and CAs have similarly relied on self-reported smoking status data, as biochemical validation of large samples is expensive and often practically prohibitive throughout pregnancy. The data in our study were from primary care and thus include self-reported smoking status that is ascertained prospectively during pregnancy by physicians, nurses, or midwives. According to some evidence, self-reports of smoking habits to health professionals invested in the person's clinical care have a reasonable level of accuracy compared with those in bespoke studies.[48]

TABLE 5 Adjusted OR for MCAs in Children According to Maternal NRT Exposure During Early Pregnancy Compared With Maternal Smoking

Variable	NRT Group (n = 2677): Adjusted OR[a,b] (99% CI)	P
All MCAs combined	1.07 (0.78–1.47)	.58
Heart	0.92 (0.52–1.62)	.72
Limb	0.95 (0.45–2.01)	.87
Genital system	1.21 (0.58–2.54)	.50
Urinary system	1.98 (0.76–5.13)	.06
Chromosomal	1.05 (0.24–4.62)	.92
Musculoskeletal	1.37 (0.53–3.54)	.39
Orofacial cleft	0.55 (0.11–2.71)	.33
Digestive system	1.17 (0.34–3.97)	.74
Nervous system	0.82 (0.20–3.41)	.72
Other malformations[c]	1.08 (0.29–3.97)	.88
Eye	0.74 (0.15–3.77)	.64
Respiratory system	3.49 (1.05–11.62)	.007
Genetic	—	—
Abdominal wall	—	—
Ear, face, and neck	—	—

—, no cases in the NRT group therefore no ORs presented.

[a] Reference category = smokers.

[b] Adjusted for maternal age at conception, Townsend deprivation index score, maternal diabetes, asthma, mental illnesses, and multiple births.

[c] Including asplenia and conjoined twins.

Interpretation in Light of Current Literature

A previous population-based Danish study assessed all CAs, including minor anomalies, at birth and the first year of life, in relation to self-reported NRT use and smoking during the first 12 weeks of pregnancy.[12] The study showed that the women who used NRT in the first 12 weeks of pregnancy and reported not smoking were more likely to have children with CAs (OR: 1.61 [95% CI: 1.01–2.58]). However, when the analysis was restricted to MCAs only, no significant association was found (OR: 1.13 [95% CI: 0.62–2.07]), which was similar to results for MCA risk in our NRT group compared with the control group (OR: 1.12 [99% CI: 0.84–1.48]). In contrast, a randomized controlled trial of the use of nicotine patches in 1050 pregnant women found a 30% reduced risk of all CAs, including major and minor anomalies in the NRT group compared with those prescribed a placebo.[13] However, the results were not significant and were based on a very small number of children with anomalies (9 children in the NRT group compared with 13 children in the placebo group). A similar reduction in the risk of CAs among women prescribed NRT was found in a more recent trial including 476 pregnant smokers from 23 maternity wards in France.[14]

We found that the odds of MCAs in the NRT group were 7% higher compared with smokers, although this finding was not statistically significant. Similarly, the absolute risks of system-specific anomalies were also generally higher than in the overall population and in smokers, although these differences were small. This finding may be due

to the fact that, in general, women who were prescribed NRT may have been heavier smokers[49,50] for all or part of their pregnancy or immediately before their pregnancy, and they found it difficult to quit without pharmacotherapy. We did not have adequate information on the smoking intensity of the women before acquiring NRT prescriptions. Therefore, it was difficult to separate the effects of smoking from the effects of NRT, which will be a limitation of any study investigating NRT and smoking exposure without detailed monitoring diaries of behavior. In addition, despite adjustments in the analysis for sociodemographic factors and maternal morbidities, unmeasured confounding factors may have contributed to the nonsignificantly higher OR point estimate for the effect of NRT exposure on MCAs overall and the statistically significant association found for respiratory anomalies. In fact, women prescribed NRT were considerably more likely to have diagnosed morbidities, particularly asthma and mental illnesses; these conditions and their related medication use have been associated with increased CA risks in some studies.[51,52] Maternal asthma and mental illnesses were more common in the NRT group compared with both smokers and control subjects (14.5%, 10.4%, and 8.2%, respectively, for asthma and 20.7%, 15.3%, and 6.9% for mental illnesses). Among the children with respiratory anomalies whose mothers were prescribed NRT, 10% had asthma compared with 7% among mothers from the control group. Asthma prevalence among women in the smoking group was also 10%, however; it is possible that asthma severity varied between groups but was difficult to ascertain. Furthermore, it is also possible that the increased risk of respiratory anomalies was a chance finding related to multiple comparisons, which is inevitable when studying all CAs. We must consider, however, that our findings could represent a true increase in the risk of respiratory anomalies because nicotine has been shown to alter fetal lung development in animal studies.[53] Nevertheless, this finding should be interpreted with caution because it was based on only 10 exposed cases among 157 total children with respiratory anomalies.

For smokers, we found no statistically significant association with MCAs in their infants compared with the control group. This finding is similar to the results from a large meta-analysis of observational studies, which found that the OR for overall CAs was 1.01 (95% CI: 0.96–1.07). The meta-analysis found a significant association between maternal smoking and heart defects (OR: 1.09 [95% CI: 1.02–1.17]) and some other system-specific anomalies.[6] Our study reported a broadly similar risk for heart anomalies (OR: 1.01 [99% CI: 0.60–1.70]), although the association was not statistically significant. A potential explanation for this finding could be the lower power of our study to assess the risk of system-specific anomalies. In addition, the meta-analysis included both prospective and retrospective (postdelivery) ascertainment of antenatal smoking status, and some included studies did not adjust for potential confounders.

CONCLUSIONS

The existing evidence on maternal NRT exposure during early pregnancy and the risk of MCAs in women's offspring is limited. The present study, with much larger numbers of children with MCAs than any previous study, also did not find a protective or harmful effect of NRT during pregnancy; the exception was an increased risk of respiratory system anomalies, but this finding was based on only 10 exposed cases. Therefore, it may be likely that there is no true association between NRT exposure during pregnancy and MCAs in the offspring. However, it is difficult to be certain in the absence of adequate statistical power and potential residual confounding; an even larger study with biochemically validated data on active and passive smoking exposures is required.

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