Effect of diuretics on fetal growth: A drug effect or confounding by indication? Pooled Danish and Scottish cohort data

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Aims The diabetogenic effect of diuretics, as well as the indication for prescribing them, may impact on fetal growth. We analysed whether the purchase of prescription drugs for diuretics during pregnancy was associated with measures of fetal growth.

Methods During 1991–98 all women who purchased prescription drugs for diuretics during pregnancy were identified in the Northern Jutland Prescription Database (NJDP), Denmark, and in the Medicines Monitoring Unit's Database (MEMO), Scotland. Information on birth weight and gestational age was obtained from the Danish Birth Registry, the Danish Hospital Discharge Registry and the Scottish Tayside Neonatal Database. Information on diabetes, hypertension and prepregnancy weight were obtained by hospital record review in a sample of women in the Danish cohort. Women who did not purchase prescription diuretics during pregnancy were used as a reference group in both cohorts.

Results Danish women who purchased prescription loop diuretics during pregnancy gave birth to infants with higher birth weights than women who did not use diuretics; mean difference 104.7 g (95% CI; 2.6, 206.9). However, the high prevalence of diabetes (10.3%) among Danish women who purchased prescription loop diuretics during pregnancy might explain this result. Both the Danish and the Scottish women who purchased prescription diuretics during their pregnancy were at increased risk of preterm delivery (<37 completed weeks); ORs: 1.8 (CI; 1.2, 2.7)$_{NJDP}$, 1.9 (CI; 0.9, 4.3)$_{MEMO}$. The proportion of hypertension among women who purchased prescription thiazides was 15.8%, and the risk of having an infant with a birth weight (BW) <2500 g was increased; ORs: 2.6 (CI; 1.4, 5.0)$_{NJDP}$, 2.4 (CI; 0.8, 7.8)$_{MEMO}$.

Conclusions Prescribing diuretics during pregnancy was associated with differences in birth weight and incidence of preterm delivery. Confounding by indication may explain the findings.

Keywords: confounding by indication, diuretics, fetal growth, pregnancy

Introduction

Diuretics, though their use is controversial, are used during pregnancy for treating hypertension and cardiac diseases [1–4]. Hypertensive disorders affect approximately 10% of pregnant women and are associated with increased perinatal and maternal mortality and morbidity [2].

The use of diuretics during pregnancy has been associated with increased birth weight [5, 6], perhaps due to the diabetogenic side-effects of these drugs [7–11]. A recent review of nine prospective randomized clinical trials of diuretics administered during pregnancy revealed

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a significant reduction in the risk of pre-eclampsia. There may therefore be beneficial effects from treating pregnancy related diseases with diuretics [12]. Diuretics given after the first trimester interfere with normal plasma volume expansion, which may exacerbate the volume depletion in pre-eclampsia and cause intrauterine growth retardation [3].

Diuretics have not been reported to have teratogenic effects. According to the US Food and Drug Administration, diuretics are classified in risk category C which comprises drugs that involve a proven or suspected, but not directly teratogenic, risk to the fetus [13]. This classification is based on reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalances following maternal treatment.

We analysed whether purchasing a prescription diuretic during pregnancy was associated with measures of fetal growth in a population-based follow-up study based on the Northern Jutland Prescription Database (NJPD), Denmark, and the Medicines Monitoring Unit's Database (MEMO), Scotland. The influence of potential confounders such as prepregnancy weight, hypertension and diabetes was evaluated by review of the hospital records for a sample of women in the Danish cohort.

Materials and Methods

We conducted two population-based follow-up studies based on the NJPD and MEMO. The methods of data collection and record-linkage of these databases have been described in detail elsewhere [1, 14].

Data sources

The Northern Jutland Prescription Database (NJPD) provided data concerning purchased prescription drugs for the Danish study. All prescribed drugs are sold through pharmacies equipped with computerized accounting systems linked to the Danish National Health Service, which refunds part of the costs of most prescribed drugs. Information on the type of drug, classified according to the Anatomical Therapeutical Chemical (ATC) classification system [15], the date of dispensing, and the customer's personal identification number is transferred electronically to the NJPD from the pharmacies when a prescription is refunded from the Danish National Health Service. We used the NJPD to identify all prescription drugs for diuretics (ATC C03) used during pregnancy by women who gave birth in the county between 1991 and 1998 ($n=47\ 313$). Information on birth weight (BW), length at birth (LB), gestational age (GA), and the mothers' cohabitation status and their reported smoking habits at the first prenatal midwife visit was obtained from the Danish Birth Registry. Information on congenital malformations was obtained from the County Hospital Discharge Registry.

The Medicines Monitoring Unit's Database (MEMO) contains information on dispensed prescriptions for all drugs from 1993 to 1995 for the 400 000 inhabitants in Tayside, Scotland. We used the database to identify all prescriptions for diuretics (ATC C03) used by pregnant women who gave birth in Tayside between 1993 and 1995 ($n=35\ 871$). Information on the BW, LB, and GA was obtained from the Neonatal Database which, like the Danish Birth Registry, includes information on all births at hospitals in Tayside from 1980 to 1997 ($n=35\ 871$). In Tayside, virtually all deliveries take place in hospital. Social status was recorded by means of the Carstairs scores, which is a deprivation measure based on data derived from the decennial census. Its component variables are the proportion of people in a postcode sector with no car, the percentage living in overcrowded housing, the percentage with the household head in semi or unskilled occupation and the percentage of men unemployed. These data are transformed into a single score for each postcode, and classified into seven categories, ranging from deprivation category 1 (most affluent) to deprivation category 7 (least affluent) [14].

Information about confounders based on hospital record review in a sample of the Danish cohort

Pre-pregnancy weight, diabetes, and hypertension are associated with birth weight. Information on these potential confounders was obtained from hospital records at the hospital of Aalborg, which hosts the only obstetrical department in the County of Northern Jutland, Denmark. Among women who gave birth at the hospital of Aalborg we reviewed hospital records from women who purchased prescription diuretics during pregnancy ($n=269$) and 80 women randomly from the reference group.

For these 349 women, comprising the 'Danish sample', we reviewed available medical records.

Definitions and analyses

Low birth weight (LBW) was defined as birth weight (BW) below 2500 g. Assessment of low birth weight at term was restricted to deliveries after the 37th week of gestation. High birth weight was defined as birth weight above 4000 g and preterm delivery was defined as birth before 37 completed weeks of gestation.

We performed analyses for women who purchased prescription diuretics (1) any time during their pregnancy and (2) during their third trimester. The reference group included women who did not purchase prescription diuretics during their pregnancy. We restricted the analyses to singleton pregnancies, since women with

multiple births were often admitted to obstetric departments during pregnancy, and we did not have information on drug use during hospital admissions. The analyses were performed for overall use of diuretics (ATC: C03) and stratified analyses were performed for ATC subgroups: loop-diuretics C03C, and thiazide diuretics C03A and C03B. We used multiple linear regression analysis to estimate the differences in mean BW, LB and GA. The associations between purchasing prescription diuretics during pregnancy and the risk of LBW, HBW and preterm delivery were estimated using logistic regression analyses. We adjusted for the mother's smoking during pregnancy (NJPD), maternal age, cohabitation status (NJPD), Carstairs scores (MEMO) and gender of the child. The analyses regarding BW and length at birth were also adjusted for GA.

Results

We identified 315 Danish and 73 Scottish women who purchased at least one prescription diuretic during pregnancy. Table 1 shows the number of women who purchased at least one prescription drug in the form of loop and thiazide diuretics.

Birth weight, length at birth and gestational age

There were no differences in mean BW or length at birth between the offspring of women who purchased any of the prescription diuretics during pregnancy and the references (Table 1). Women who bought prescription diuretics had a higher incidence of preterm delivery; ORs 1.8 (95% CI; 1.2, 2.7)$_{\text{NJPD and}}$ 1.9 (95% CI; 0.9, 4.3)$_{\text{MEMO}}$ (Table 1).

The stratified analyses showed that mean BW and length at birth differed within ATC groups. Purchasing prescription thiazide diuretics was associated with an increased risk of having a LBW infant (Table 1). On the contrary, the mean BW was 105 g higher (95% CI; 3, 207) among Danish women who purchased prescription loop diuretics; 25% of the offspring of these women weighed more than 4000 g. When we restricted analysis to term deliveries and prescription diuretics purchased during the third trimester, the adjusted difference in mean BW among the offspring of Danish women who used loop diuretics and references was 113 g (95% CI; 25, 251).

Malformations

Malformations were identified in seven cases (9.0%) among women who bought prescription diuretics during the first 8 weeks of gestation and in 2235 cases (4.8%) among the 46 998 controls; OR: 1.9 (95% CI; 0.9, 4.3). Malformations were found in five cases (11.5%) who had bought prescription loop diuretics and in three cases (8.6%) who had bought thiazides: ORs: 2.2 (95% CI; 0.5, 9.6) and 1.9 (95% CI; 0.8, 4.7). The malformations were (1) polydactyly and cleft lip, (2) dislocation of the hip, (3) patent ductus arteriosus (expected since 26th week of GA), (4) incomplete development of a finger, (5) congenital drop lid, (6) syndactyly of the hand and patent ductus arteriosus, (7) nonspecific congenital malformation. Diabetes was present among three of the mothers who had a baby with malformations.

Table 1 Mean birth weight, and proportion of low birth weight, high birth weight and preterm birth among the offspring of 315 Danish and 73 Scottish women who purchased diuretics during pregnancy.

	Birth weight (g)		*Low birth weight*		*High birth weight*		*Preterm birth*	
n *in ATC groups*	$Mean_{s.d.}$	*Mean diff*$^{\star 1-5}_{95\%\ CI}$	$number_{\%}$	$OR^{\star 1-3}_{95\%\ CI}$	$number_{\%}$	$OR^{\star 1-3}_{95\%\ CI}$	$number_{\%}$	$OR^{\star 1-3}_{95\%\ CI}$
NJPD, Denmark								
Reference population = 46,998	3510.2		720 1.5		8957 19.1		2482 5.3	
Overall $n = 315$	3439.8 719.5	26.6 −25.2, 78.4	10 3.2	1.7 1.1, 2.7	63 20.0	1.1 0.8, 1.4	32 10.2	1.8 1.2, 2.7
Loop $n = 83$	3570.8 732.9	104.7 2.6, 206.9	0	–	21 25.3	1.3 0.7, 2.1	9 10.8	1.6 0.7, 3.7
Thiazide $n = 232$	3401.3 712.4	6.5 −53.7, 66.2	10 4.3	2.6 1.4, 5.0	42 18.1	1.0 0.7, 1.4	23 9.9	1.9 1.2, 3.0
MEMO, Scotland								
Reference population = 35,798	3394.1 562.9		749 2.1		4509 12.5		1854 5.2	
Overall $n = 73$	3318.5 550.1	−48.7 −151.2, 53.8	4 5.5	1.8 0.7, 5.1	7 9.6	0.7 0.3, 1.6	7 9.6	1.9 0.9, 4.3
Loop $n = 31$	3237.1 515.4	−117.7 −273.8, 38.5	1 3.2	1.0 0.1, 7.8	1 3.2	0.2 0, 1.6	4 12.9	2.7 1.0, 7.9
Thiazide $n = 42$	3378.6 573.1	−3.4 −132.4, 139.3	3 7.1	2.4 0.8, 7.8	6 14.3	1.1 0.5, 2.7	3 7.1	1.4 0.4, 4.6

Number of women who used diuretics during pregnancy are given as *overall* (ATC C03) and within ATC groups; *loop* diuretics (ATC C03C) and thiazide (ATC C03A and C03B). Crude values of birth weights are given as mean values with standard deviations (s.d.). Crude values of low birth weight, high birth weight and preterm delivery are given as numbers and percentages. Analyses adjusted for maternal age$^{\star 1}$, smoking$^{\star 2}$ (NJPD), cohabitation status (NJPD) and Carstairs scores (MEMO)$^{\star 3}$, gender of the child$^{\star 4}$ and gestational age in completed weeks$^{\star 5}$. Results from these analyses are given as mean differences and ORs with 95% confidence intervals (CI).

Analyses based on medical record review in a sample of the Danish cohort

Information on prepregnancy weight, diabetes and hypertension were obtained for 234 (67.1%) of the 349 women in the Danish sample. We were able to locate medical files for 234 (67.1%) of the 349 women in the Danish sample. Medical files were available for 234 (67.1%) of the 349 women in the Danish sample. The number of medical files available for the 269 women who redeemed prescriptions for diuretics during pregnancy and gave birth at the hospital of Aalborg was 185 (67.1%) and 49 (61.3%) for the 80 controls. For the remaining 115 women in the sample information were incomplete or hospital records not available. Pre-pregnancy weight was higher among women who purchased prescription loop ($n=39$) and thiazide ($n=146$) diuretics during pregnancy than among the references ($n=49$), the mean difference was 9.1 kg for loop diuretics and 8.3 kg for thiazide diuretics. No women with diabetes or hypertension were found in the reference group. Among women who bought prescription loop diuretics during their pregnancy ($n=39$), 10.3% suffered from diabetes and 7.7% from hypertension. Similarly, among those ($n=146$) who bought prescription thiazide diuretics, 5.5% suffered from diabetes and 15.8% from hypertension. The mean BW of offspring of women with diabetes ($n=12$) was 3974 g (s.d.; 940). The mean BW of offspring of women with hypertension ($n=26$) was 2987 g (s.d.; 1088).

Discussion

The purchase of prescription thiazide diuretics was associated with an increased risk of LBW while prenatal use of loop diuretics led to an increase in the mean BW of the offspring. However, the prevalence of diabetes was high among Danish women who purchased prescription loop diuretics during pregnancy. Women who used diuretics during pregnancy were at increased risk of preterm delivery and purchasing prescription diuretics was associated with an increased risk of malformations in the offspring. Yet the present study is not large enough to establish the drug-associated risk for specific malformations.

The strengths of our design lie in the completeness of data registration, the prospectively collected dispensing data, and the possibility of comparing results from two different cohorts. Both prescription databases are based on purchased prescription drugs, thus by-passing primary noncompliance. It was also possible to obtain information from hospital records on confounding factors for 269 Danish women. The limitations of our study are that our data did not include information on drug use during hospital admission or any clinical details. Furthermore, we have no information on compliance, and the only information on timing of exposure is the computer recorded date of dispensing.

The Danish and Scottish data revealed consistent results regarding the association of preterm delivery and LBW with the use of diuretics during pregnancy. This is in agreement with the few previous studies on the relation between the use of diuretics during pregnancy and fetal growth [3, 16, 17]. Pregnant women with chronic or severe gestational hypertension have a higher risk of progression to toxemia and fetal growth retardation [2, 4, 18]. The increased risk of having a LBW infant in our study was found only among women who used thiazide diuretics. Among these women the prevalence of hypertensive disorders was highest. Thus, the increased risk of LBW and preterm delivery in this study may be linked to the indication for prescription rather than to the treatment itself, e.g. confounding by indication may explain the result. Sibai *et al.* [3] found no differences in GA or BW among 20 women with mild long-term hypertension randomized to continuation or discontinuation of diuretic treatment, although the plasma volume expansion was decreased among women who continued diuretic treatment during pregnancy.

The mean BW was increased among the offspring of Danish women who purchased prescription loop diuretics during pregnancy. This is in agreement with a study conducted by Czeizel who found a higher mean BW among the offspring of women who used frusemide during pregnancy [5]. A reduction in BW following prenatal exposure to diuretics has also been reported [3]. Based on additional information from hospital records, we find that the differences in mean BW may be explained by diabetes, hypertension and prepregnancy weight. Thus, our result may be explained by indications rather than by drug effects [10, 11, 19]. Furthermore, the increased BW associated with purchasing prescription drugs for loop diuretics could not be reproduced in the Scottish data set.

We found an increased risk of different malformations among the offspring of women who purchased prescription diuretics during early pregnancy. We do not find the increased risk of malformations to be suggestive of causal drug effects since no known teratogens uniformly increase the risk of all malformations. Malformations remain the major cause of morbidity and mortality among the offspring of women with diabetes [20]. The high prevalence of diabetes in this study is likely to explain the increased risk of malformations. There are no reports of teratogenic effects of loop or thiazide diuretics, and studies on the relation between diabetes and malformations are few [21].

In conclusion, we found that purchasing prescription diuretics during pregnancy was associated with BW and preterm delivery. The results concerning BW were not

consistent in the two data sets. Furthermore, analyses based on additional information obtained from hospital records indicated that confounding by indication may explain the result. Our study indicates that confounding by indication may lead to wrong conclusions in studies based solely on registry data.

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References

1 Olesen C, Steffensen FH, Nielsen GL, de Jong van den Berg LT, Olsen J, Sørensen HT. Drug use in first pregnancy and lactation. A population-based survey among Danish women. *Eur J Clin Pharmacol* 1999; **55**: 139–144.

2 National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 1990; **163**: 1691–1712.

3 Sibai BM, Grossman RA, Grossman HG. Effects of diuretics on plasma volume in pregnancies with long- term hypertension. *Am J Obstet Gynecol* 1984; **150**: 831–835.

4 Ferris TF. Pregnancy complicated by hypertension and renal disease. *Adv Intern Med* 1990; **35**: 269–287.

5 Czeizel AE, Toth M. Birth weight, gestational age and medications during pregnancy. *Int J Gynaecol Obstet* 1998; **60**: 245–249.

6 Tervila L, Vartiainen E. The effects and side effects of diuretics in the prophylaxis of toxaemia of pregnancy. *Acta Obstet Gynecol Scand* 1971; **50**: 351–356.

7 Wolff WF, White K, Okun R. Drug-induced diabetes. *JAMA* 1963; **185**: 568–574.

8 Chan JC, Cockram CS, Critchley JA. Drug-induced disorders of glucose metabolism. *Mechanisms Manage Drug Saf* 1996; **15**: 135–157.

9 Taylor R. Drugs and glucose tolerance. *Adv Drug React Bull* 1986; **121**: 452–455.

10 Dornhorst A, Powell SH, Pensky J. Aggravation by propranolol of hyperglycaemic effect of hydrochlorothiazide in type II diabetics without alteration of insulin secretion. *Lancet* 1985; **1**: 123–126.

11 Amery A, Berthaux P, Bulpitt C, *et al*. Glucose intolerance during diuretic therapy. Results of trial by the European Working Party on Hypertension in the Elderly. *Lancet* 1978; **i**: 681–683.

12 Collins R, Yusuf S, Peto R. Overview of randomised trials of diuretics in pregnancy. *Br Med J* 1985; **290**: 17–23.

13 Briggs GG, Freeman RK, Summer JY. In *Drugs in Pregnancy and Lactation* ed. Mitchell CW. 1997.

14 Evans JM, MacDonald TM. Record-linkage for pharmacovigilance in Scotland. *Br J Clin Pharmacol* 1999; **47**: 105–110.

15 Drug utilization studies. Methods and uses. Introduction, 1st edition. WHO Regional Publications, European Series, no. 45, 1993.

16 Gant NF, Madden JD, Shteri PK, MacDonald PC. The metabolic clearance rate of dihyroisoandrosterone sulfate. IV. Acute effects of induced hypertension, hypotension, and natriuresis in normal and hypertensive pregnancies. *Am J Obstet Gynecol* 1976; **124**: 143–148.

17 Christianson R, Page EW. Diuretic drugs and pregnancy. *Obstet Gynecol* 1976; **48**: 647–652.

18 Brazy JE, Grimm JK, Little VA. Neonatal manifestations of severe maternal hypertension occurring before the thirty-sixth week of pregnancy. *J Pediatr* 1982; **100**: 265–271.

19 Sandstrom PE. Evidence for diabetogenic action of bumetanide in mice. *Eur J Pharmacol* 1988; **150**: 35–41.

20 Reece EA. Maternal fuels, diabetic embryopathy: pathomechanisms and prevention. *Semin Reprod Endocrinol* 1999; **17**: 183–194.

21 Gilstrap LC, Little BB. Cardiovascular drugs during pregnancy. In *Drugs and Pregnancy* eds Gilstrap LC, Little BB. London: Chapman & Hall, 1997: 87–90.