

Papers

Use of clomifene during early pregnancy and risk of hypospadias: population based case-control study

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Clomifene is widely used for inducing ovulation.¹ It is structurally related to diethylstilbestrol, which has been linked to vaginal and cervical clear cell adenocarcinoma in women exposed in utero. The adverse effect is less severe in sons, although links to testicular cancer and urogenital anomalies, such as epididymal cysts, have been reported.^{2,3} A recent study also found an increased risk of hypospadias in the sons of women exposed to diethylstilbestrol in utero.⁴ Clomifene has a half life of about five days, but its metabolites have been found in blood samples on day 22 of the menstrual cycle and in faeces up to six weeks after administration.⁵ The occurrence of hypospadias may be increasing. Little is known about the risk of hypospadias in boys born to women who have used clomifene to induce ovulation.

Methods and results

Our case-control study was done in the Danish counties of North Jutland, Aarhus, Viborg, and Ringkjøbing (population 1.6m, with 65 383 male births in the study period: 1989 to 2002, North Jutland 34 859; 1996-2002, Aarhus 20 382; and 1998-2002, Viborg 4148 and Ringkjøbing 5 994).

We identified all cases of hypospadias that had a full prescription history in the period 1989-2003 from the Danish hospital discharge registry, which contains all discharges from hospitals in Denmark since 1977 and includes 10 digit personal identifiers, surgical procedures, and up to 20 discharge diagnoses classified according to ICD-8 (international classification of diseases, eighth revision) until the end of 1993 and ICD-10 after 1993. The codes for hypospadias in ICD-8 are 752.20, 752.21, 752.22, 752.28, and 752.29; in ICD-10, the codes are Q54.0, Q54.1, Q54.2, Q54.3, Q54.4, Q54.8, and Q54.9.

We found a total of 319 cases of hypospadias (any time post-partum) in the four counties. From the Danish birth registry,

which contains information on all births in Denmark since 1 January 1973, we selected a control group of 10 records of male births without a diagnosis of hypospadias and with a full prescription history during the same period. We matched cases and controls for birth month, birth year, and county of residence of the child.

The Danish national health service reimburses part of patients' expenditure on many prescribed drugs, including clomifene. The four counties have pharmacies equipped with electronic systems that record information on the drug, dose, personal identification number, and date of dispensing of the drug. All data are transferred to a research database at Aarhus University Hospital. The data from the four counties are electronically available from 1 January 1989 (North Jutland), 1 January 1996 (Aarhus), and 1 January 1998 (Ringkjøbing and Viborg). We took data on all prescriptions for clomifene during the first trimester and 90 days before conception. To avoid confounding, we also took data about prescriptions for antidiabetic drugs and antiepileptic drugs and we also collected data on pre-eclampsia, as it has been associated with hypospadias. We used conditional logistic regression adjusted for available variables to estimate the relative risk for hypospadias after exposure to clomifene. We found an adjusted odds ratio of 0.48 (95% confidence interval 0.15 to 1.54) for hypospadias associated with clomifene (table). Restricting the exposure to clomifene to the first trimester and up to 30 days before the time of conception did not change the risk estimate substantially.

Comment

Clomifene was not associated with any increased risk of hypospadias. Several factors should be taken into account when interpreting this study. The full and independent registration of

Characteristics of 319 boys with hypospadias whose mothers used clomifene during early pregnancy and 3190 population controls

	No (%) of cases	No (%) of controls	Crude odds ratio	Adjusted odds ratio (95% CI)*
Prescription for clomifene†	3 (0.9)	59 (1.8)	0.51	0.48 (0.15 to 1.54)
Maternal age (years):				
<25	57 (17.9)	459 (14.4)	1	1
25-30	144 (45.1)	1460 (45.8)	0.80	0.84 (0.61 to 1.17)
>30	118 (37.0)	1271 (39.8)	0.75	0.85 (0.59 to 1.22)
Birth order:				
1	155 (48.6)	1326 (41.6)	1	1
>1	164 (51.4)	1864 (58.4)	0.76	0.79 (0.62 to 1.02)
Maternal pre-eclampsia†	18 (5.6)	71 (2.2)	2.57	2.43 (1.43 to 4.12)
Maternal epilepsy†	3 (0.9)	23 (0.7)	1.31	1.32 (0.39 to 4.49)
Maternal diabetes†	2 (0.6)	10 (0.3)	2.00	2.01 (0.44 to 9.21)

*Adjusted for the other variables in the table.

†Reference group is women not exposed to clomifene.

What is already known on this topic

The prevalence of hypospadias may be increasing

Clomifene is structurally related to diethylstilbestrol, which has been linked to urogenital anomalies and testicular cancer in males exposed in utero, and possibly to hypospadias in male offspring of women exposed to diethylstilbestrol in utero

What this study adds

This large population based case-control study does not provide any evidence that clomifene is a risk factor for hypospadias

births, birth outcome, and prescriptions prevented selection bias and some types of information bias as this study was based on routinely recorded data. Any non-compliance with the use of clomifene, however, might bias the estimates of risk towards the null.

Contributors: HTS developed the idea and designed the study together with LP and MVS. LP, MVS, MN, and BN collected and validated the data. LP, MVS, and HTS analysed the data. HTS wrote the first draft. EEH, LP, MVS, MN, and BN critically revised the paper. HTS is guarantor.

Funding: Western Danish Research Forum for Health Sciences.

Competing interests: None declared.

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(Accepted 9 November 2004)

doi 10.1136/bmj.38326.606979.79

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