Outcome of 100 pregnancies initiated under treatment with cabergoline in hyperprolactinaemic women

Journal:	<i>Clinical Endocrinology</i>
Manuscript ID:	CEN-2010-000087.R1
Manuscript Type/Office:	2 Original Article - Europe, excluding UK
Date Submitted by the Author:	07-Apr-2010
Complete List of Authors:	Lebbe, Marie; Cliniques Universitaires St Luc, Endocrinology Hubinont, Corinne; Cliniques Universitaires St Luc, Obstetrics Bernard, Pierre; Cliniques Universitaires St Luc, Obstetrics Maiter, Dominique; Cliniques Universitaires St Luc,UCL, Endocrinology
Key Words:	hyperprolactinaemia, Pregnancy, dopamine agonist, cabergoline, prolactinoma, congenital malformation

Outcome of 100 pregnancies initiated under treatment with cabergoline in hyperprolactinaemic women

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Short title: Cabergoline therapy and outcome of pregnancy

Key words: Hyperprolactinaemia, prolactinoma, pregnancy, dopamine agonist, reproduction, congenital malformation.

Disclosure statement: The authors have nothing to declare

Word Count: Abstract 248, Text 3364, 20 References; 2 Figures; 3 Tables

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Abstract

Context: Data concerning the safety for pregnancy of cabergoline treatment in hyperprolactinaemic women are still scarce.

Objective: To exclude a higher than normal risk for miscarriage and congenital malformation in pregnancies initiated under cabergoline treatment.

Design: A retrospective study of 100 pregnancies in 72 hyperprolactinaemic women treated with cabergoline at the time of conception and follow-up of the 88 born children.

Methods: Cabergoline was interrupted in 99 pregnancies and continued in one case. Foetal exposure dose to cabergoline was calculated for each pregnancy. Complications of pregnancy and neonatal status were compared to those observed in an age-and delivery time-matched control group of 163 women.

Results: The mean foetal exposure dose to cabergoline was 3.6 ± 4.7 mg. The rate of spontaneous miscarriages was 10%. Three medical terminations of pregnancy were performed for a foetal malformation (3%). Minor to moderate complications were observed in 31% of the pregnancies, a figure similar to that found in the control group. An increase in tumour size (2-8 mm) was observed in 17/37 evaluated cases, needing re-introduction of cabergoline during pregnancy in 5 patients. The 84 deliveries resulted in 88 infants, 3 of them presenting with a malformation (3.4%). Neonatal status was comparable to the control group, where a malformation rate of 6.3% was observed. Postnatal development of the children was normal.

Conclusion: Cabergoline treatment at the time of conception appears to be safe for both the pregnancy and the neonate, although more data are still needed on a larger number of pregnancies.

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Introduction

Dopamine agonists represent the first-line treatment of hyperprolactinaemia, a frequent endocrine disorder of the hypothalamic-pituitary axis, prevailing in young women of reproductive age.⁽¹⁾ Nowadays, the most commonly used drug is cabergoline, which has potent long-lasting prolactin-lowering effects and is often better tolerated and more efficient than bromocriptine.⁽²⁻⁶⁾ One frequent goal of medical therapy is to restore gonadal function in hyperprolactinaemic women,⁽⁷⁾ and patients may wish to conceive while being treated with this drug. Previous investigations in humans have indicated that bromocriptine may cross the placental barrier and can be found in dose-related concentrations in the foetal blood and amniotic fluid.⁽⁸⁾ Although not formally demonstrated, it is likely that this property also holds true for cabergoline. As foetal exposure is likely during the first weeks of gestation, a critical period for organogenesis, it is essential to ascertain that these drugs do not have adverse effects on the course and outcome of pregnancy or on the postnatal development of the offspring exposed *in utero*.

The safety of bromocriptine for both the mother and the foetus has been demonstrated in more than 6,000 pregnancies, showing rates of spontaneous abortions (11%) and neonatal malformations (3.5%) similar to those quoted for a normal population.⁽⁹⁻¹¹⁾ In contrast, published data regarding the safety of cabergoline are still scarce, being available for less than 400 pregnancies.⁽¹²⁻¹⁴⁾ These studies reported no significant increase in the rate of miscarriage or congenital malformations, but it is still of concern whether a treatment with cabergoline during the early stages of pregnancy can result in a higher than normal risk of congenital malformation. Therefore, the aim of our study was to extend previously reported results by collecting information on 100 pregnancies occurring in 72 women treated with cabergoline at the time of conception. We also gathered follow-up data on the psycho-motor development of the 88 born infants.

Patients and methods

Patients

We retrospectively reviewed the medical files of 100 consecutive pregnancies initiated between 1997 and 2009 in 72 hyperprolactinaemic women taking cabergoline at the time of conception. The median age at diagnosis of hyperprolactinaemia was 28.5 ± 5.6 years (range: 14.2–40.0), and median prolactin concentration at diagnosis was $67.3 \mu\text{g/l}$ (range: 25.9–875.2 $\mu\text{g/l}$, normal values < 20). The initial diagnosis was a pituitary microprolactinoma in 45 women (62%), a macroprolactinoma in 15 (21%) and idiopathic hyperprolactinaemia in 12 patients (17%). Data on tumour size at diagnosis were available for all adenomas, with a maximal diameter ranging from 3 to 27 mm. Seven patients had previously undergone pituitary surgery with persistent hyperprolactinaemia in 4 and later recurrence in 3 patients.

In order to obtain a comparative control group, we blindly selected for every delivery included in our study (cabergoline group, $n=84$), two mothers out of the obstetrical register of our institution ($n = 168$), who were matched for age and date of the delivery. Thereafter, we excluded from this control group pregnant women specifically referred from another hospital for a high risk pregnancy ($n=3$) or a foetal malformation ($n=2$), so the final number of controls was 163. We also compared our data with a regional Belgian register which includes data on the follow-up of 59,253 pregnancies in Flanders in 2003.⁽¹⁵⁾

Study design

All patients had been advised to stop cabergoline treatment as soon as the pregnancy was confirmed but for several reasons, some women continued their treatment for a longer period, during 10–12 weeks of gestation in 8 cases, beyond the first trimester [15–22 weeks] in 4 and until delivery in one case. Information on cabergoline exposure prior to and during pregnancy and on the dose at discontinuation was recorded. The cumulative foetal cabergoline

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exposure dose was derived from the product of the dose at discontinuation by the calculated gestational period until interruption of the treatment.

For each woman, we obtained details on her previous reproductive history, date of her last menstrual period, type of conception: spontaneous or by in vitro fertilization (IVF), use of other medications at the time of conception, occurrence of spontaneous miscarriage, and voluntary or medical terminations of pregnancy (TOP). We also collected information on occurrence of headaches, visual disturbances, hypertension, gestational diabetes, infection or any other illness during pregnancy. As a routine procedure followed in our centre since 20 years, and after obtaining oral informed consent of the patient, a pituitary MRI without contrast injection was performed between 24 and 32 weeks of gestation in most women with an adenoma larger than 5 mm at diagnosis (n=37).

Date, type and complications of delivery were recorded, as well as data concerning birth weight and length, Apgar score at 5 min, need of neonatal intensive care and presence of malformation. We also retrospectively examined duration of breastfeeding, re-occurrence of normal menstrual periods, post-partial persistence of hyperprolactinaemia and re-initiation of cabergoline therapy.

In a prospective post-natal study, we gathered information on the psychomotor and verbal development of the 88 born children by a personal telephone interview with the mother, performed between 2 months and 12 years after birth. Several pre-defined questions were asked, related to the age of acquisition by each child of well-characterized developmental milestones, according to a simplification of the Denver-II developmental screening test.¹⁶ Briefly, these developmental stages included the sitting down position (normal age < 9 months), first steps (18 months), autonomous walk (18 months), first comprehensive words (18 months), fluent speech and faeco-urinary continence (48 months). We also inquired about the occurrence of any serious physical illness or behavioural disorders, or need for psychological

or logopedic assistance. Prior informed consent was obtained from all mothers included in this study.

Statistical analyses

Statistical analyses were carried out using the SAS statistical software, version 16.0 (SAS Institute Inc., Cary, NC, USA). Sub-groups of cabergoline-treated pregnant women were compared using Student's t-tests for normally distributed variables and by Mann-Whitney U-tests for non-normally distributed variables. Differences in the cabergoline weekly dose at conception, in treatment duration during pregnancy, or in the cumulative foetal exposure dose to the drug between pregnancies with and without miscarriage or malformation were tested by logistic regression analyses. To compare frequencies of events between the cabergoline group (cases) and the controls, multiple logistic regression models were performed. The regression parameters and their variances were estimated using the generalized estimation equation which adjusts for the clustering of the data due to matching. The covariates in the multiple regression analysis were case, in vitro fertilization, history of abortion and previous co-morbidity.

Results

Foetal exposure dose

The median duration of cabergoline treatment prior to pregnancy was 12 months (range 0.5-113 months). Cabergoline treatment was interrupted in 99 of the 100 pregnancies, after a median period of 4 weeks after the date of conception (range: 1-22 weeks). The median dose at discontinuation was 0.5 mg/week (less than 0.5 mg/week in 23 women, 0.5 mg/week in 51, 1.0 mg/week in 25, and 1.5 mg/week in 1). One woman bearing an 18 mm-macroprolactinoma decided to continue cabergoline throughout pregnancy at the dose of 1 mg/week. The mean foetal exposure dose to cabergoline was 3.6 ± 4.7 mg (median: 2.0 mg; range: 0.5-38.0 mg).

Pregnancies

The mean age at conception was 31.8 ± 5.1 years (range: 20-43). Twenty % of the pregnancies were obtained through IVF, and 22 % of the women were taking a medication other than cabergoline at the time of conception (L-thyroxine in 16/22). Of the 100 pregnancies, 84 ended in live deliveries and 16 ended in miscarriages or abortions (Figure 1). In one case, there was a selective medical interruption of a twin pregnancy with live birth of the other baby, so that the total number of foetal losses was 17. There were 10 spontaneous miscarriages occurring between the 5th and the 16th gestational week. These pregnancies had begun at an older age (37.3 ± 2.8 years) than pregnancies without miscarriage (31.2 ± 5.0 years; $p < 0.001$). The occurrence of spontaneous miscarriage was not influenced by the dose of cabergoline at conception (0.69 ± 0.33 and 0.56 ± 0.28 mg/week), by the time at which the drug was withdrawn (4.1 ± 1.7 and 6.0 ± 5.2 weeks after conception), or by the cumulative foetal exposure dose to the drug (2.7 ± 1.6 and 3.7 ± 4.9 mg in pregnancies with and without miscarriage, respectively, NS for all three parameters by logistic regression analysis).

There were 2 voluntary abortions for unwanted pregnancy and 2 cases of ectopic pregnancy. Three medical TOP were performed between 17 and 20 weeks of gestation for a foetal malformation. These included one case of genetically confirmed Down's syndrome (cabergoline exposure dose: 6.0 mg), one case of rhombencephalo-synapsis (exposure dose: 0.5 mg) and one case of severe hydrocephaly with extended spina bifida occurring in one of the two foetuses of a clomiphene-induced dichorionic twin pregnancy and leading to a selective elimination of the anomalous foetus (cabergoline exposure dose: 4 mg).

We observed a total of 36 minor and 2 major complications in 31 pregnancies (31%) including hypertension in 3%, gestational diabetes in 4%, and preterm labour in 11% of the pregnancies. The two severe adverse events were a pre-eclampsy requiring earlier delivery and an ovarian torsion treated by surgery. In the control group, 56 complications of pregnancy were reported in 47 of the 163 women (29%). The incidence of complications was not significantly different between the cabergoline and control groups (Table 1).

Evolution of pituitary adenomas during pregnancy

A pituitary MRI without contrast injection was performed during pregnancy in 37 women with a pituitary adenoma measuring more than 5 mm at diagnosis (Figure 2). Among them, 17 (46%) showed some degree of tumour enlargement, with a median increase in height of 4 mm (range: 2-8 mm). When excluding 3 patients who continued cabergoline treatment beyond the 20th week of pregnancy (see Figure 2), a tumour growth during gestation was observed in 8/12 macroprolactinomas (median increase: + 3.0 mm) and in 9/22 microprolactinomas (median increase: + 0.5 mm). These differences did not reach statistical significance. In 5 cases (2 micro and 3 macroprolactinomas), this increase was judged significant by the clinician as the adenoma contacted the optic chiasm, and cabergoline treatment was reintroduced between the 24th and the 30th week (Figure 2). Concomitantly,

severe headaches were observed in 3/5 patients. Medical treatment allowed a rapid relief of symptoms and a significant tumour shrinking in each case (tumour height < 10 mm at control MRI performed before the end of gestation in 2 cases and after delivery in 3 cases).

Deliveries

Of the 84 deliveries, all were live deliveries. Four (5%) involved the birth of twins yielding a total of 88 infants, and two of the twin pregnancies were induced by IVF. Eight deliveries (9%) were preterm, occurring between 30 and 36 weeks. There were 66 vaginal deliveries (5 assisted because of inefficient labour) and 18 caesarean sections, for obstetrical reasons in 10 and as emergencies in 4 women (4 because of foetal distress, 4 for inefficient labour). When comparing the characteristics of deliveries between the control and cabergoline group, the proportions of assisted vaginal deliveries and of preterm deliveries were higher in the controls ($p<0.025$, Table 1).

Sixty-two women (74%) could breastfeed normally for a median period of 20 weeks (range 1-68 weeks), and sixty-three (75%) had normal reappearance of their menses after delivery and/or breastfeeding. In 52 cases (62%), hyperprolactinaemia was still observed after a time interval of 3 to 16 months after delivery and cabergoline treatment had to be re-initiated.

Neonatal status

The median birth weight of the 88 neonates was 3259 g (range 1800 – 4815 g), and the majority of the infants (68/88, 77%) had a normal birth weight of 2500-4000 g (Table 2). Neonatal malformations were observed in 3 children (3.4%) and included one case each of congenital deafness due to bilateral dilation of the vestibular aqueducts, lack of bones and muscles in the thumb of the right hand, and left uretero-hydronephrosis. The foetal exposure dose to cabergoline in these children was 0.50, 0.75 and 6.0 mg, respectively.

The cabergoline dose at conception, the duration of treatment during pregnancy and the cumulative foetal exposure dose to cabergoline were not different between pregnancies resulting in normal babies (0.56 ± 0.28 mg; 6.1 ± 5.4 weeks and 3.7 ± 4.8 mg, respectively; $n=81$) and those complicated by foetal or neonatal malformations (0.65 ± 0.38 mg, 4.3 ± 1.6 weeks and 3.3 ± 2.5 mg, respectively; $n=6$; NS for all three parameters by logistic regression analysis). The median age of the mother at conception was higher in case of neonatal or foetal malformation (34.5 years; range: 26-40, $n=6$), compared with women giving birth to normal children (31.0 years, range: 20-43, $p<0.05$). There was no significant difference in the neonatal status between the cabergoline and control groups, including similar rates of malformation, taking or not into account chromosomal anomalies (Table 2). Information on the neonatal malformations diagnosed in the cabergoline and control groups is detailed in Table 3. No specific cluster of anomalies was detected in either group.

Post-natal development of the children

At the time of the telephone interview with the mother, the children were aged between 2 months and 12 years. Seventy of them (82%) were older than 18 months and all of them could pronounce comprehensive words and walk alone at this age. Fifty children (59%) were older than 48 months and one single mother reported a slight retardation in verbal fluency at this age in her 2 sons (4%), while some difficulty for one child to reach complete continence before the age of 48 months was also reported (2%). These frequencies are similar to those found in the normal population.

Discussion

In this study on 100 pregnancies conceived under cabergoline treatment for hyperprolactinaemia, we show an incidence of spontaneous miscarriage of 10%, termination of pregnancy for a foetal malformation in 3%, and a neonatal malformation rate of 3.4%. These results are in agreement with the data reported in three previous studies on this issue. Robert *et al* monitored 226 cabergoline-induced pregnancies and reported rates of 10.6% of spontaneous miscarriage and 4.7% of neonatal malformation.⁽¹²⁾ Later, Ricci *et al* added the experience from 61 cabergoline-facilitated pregnancies, showing 9.8 and 4.1% incidences of miscarriage and neonatal malformations, respectively.⁽¹³⁾ Finally, Colao *et al* extended in 2008 the results of Robert *et al*, adding data on 154 pregnancies in women taking cabergoline, and reported on the total cohort miscarriage and malformation rates of 9.1 and 9.2%, respectively.⁽¹⁴⁾ All studies concluded that these frequencies of miscarriage and malformation were similar to rates observed in the general population, but none of these studies included a control group.

The occurrence of spontaneous miscarriage in our series (10%) is not only consistent with previous reports on this issue, but also similar to the 10.9% incidence found in the literature for the general European population.⁽¹⁷⁾ Furthermore, the occurrence of spontaneous miscarriage was not influenced by the foetal cabergoline exposure dose or by the time at which the drug was withdrawn after conception, but was related to an older age of the mother at the time of conception, which is a well known risk factor for early termination of pregnancy.

The prevalence of minor and major adverse events occurring during cabergoline-initiated pregnancies was similar to that observed in the control group. The rate of gestational diabetes in the cabergoline group (4%) was higher than the rate of 1.4% reported in the regional Flanders register,⁽¹⁵⁾ but in accordance with the 3.7% incidence noted in the control group of age-matched patients. This increased frequency is most likely due to the higher age of our pregnant women, which is a risk factor for glucose intolerance during pregnancy. There

was also no particular complication during delivery compared to the general population. The frequency of premature births was consistent with national data. Also, the distribution of birth weight and the incidences of low birth weight and intra-uterine growth retardation were comparable to those reported in the normal population. There was no case of stillbirth or neonatal mortality.

The neonatal malformation rate observed in the babies born from cabergoline-treated mothers was 3.4% in our study, a rate similar to that previously reported for bromocriptine-facilitated pregnancies and lower than rates previously reported for cabergoline-initiated pregnancies, which varied between 4.1% and 9.2%. However, it would be legitimate to also take into account the three fetuses aborted for medical reasons in our study. Adding them to the 88 infants born would bring the real incidence of malformations up to 6.6%. This figure is clearly higher than the 2.2% incidence reported by the EUROCAT Register in 2004-2005, which contains data recorded in different European countries and includes life births, stillbirths and medical terminations of pregnancies.⁽¹⁸⁾ It is however similar to the malformation rate of 6.3% observed in the control group, representing a population of mothers of identical age but not treated with the dopamine agonist. This highlights the fact that maternal age is an important confounding factor in the estimation of the malformation rate.

Another possible risk factor for a higher than expected foetal malformation incidence is the high prevalence of pregnancies issued from in vitro fertilization (20%), although none of our patients with IVF-induced pregnancy gave birth to a child with malformation. Several women had a history of miscarriage or long-standing infertility, which also could be associated with a higher occurrence of malformation. Other findings argue against a teratogenic effect of cabergoline. First, we could not identify a specific cluster of foetal defects or anomalies in our series. Furthermore, no relationship could be observed between dose and duration of exposure

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3 to cabergoline *in utero* and the occurrence of foetal or neonatal malformation. Finally, when
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5 chromosomal anomalies were excluded, the calculated malformation rate fell to 5.5%.
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8 While some degree of pituitary tumour enlargement during pregnancy was observed in
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10 45% of the evaluated cases (in 65% of untreated macroprolactinomas and in 40% of
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12 microprolactinomas), a significant increase in height requiring the reintroduction of
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14 cabergoline was not common, observed in only 5 (14%) of the 37 women who had an MRI
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16 performed during the second half of their pregnancy. Interestingly enough, such event occurred
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18 not exclusively in patients with a macroprolactinoma, but also in two women bearing a 6 mm-
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20 microadenoma before pregnancy. Both were complaining of headaches since mid-pregnancy.
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22 In each case, cabergoline treatment was effective and no further complication was observed
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24 until delivery.
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29 In the absence of a dopamine-agonist treatment, most mothers could breastfeed
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31 normally. Although breast stimulation and suckling enhance prolactin release, there is no
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33 evidence that breastfeeding has an adverse effect on recurrence of hyperprolactinaemia or
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35 tumour growth.⁽¹⁹⁾ A normal reappearance of menses was observed in three quarters of the
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37 women, whereas a recurrence or persistence of hyperprolactinaemia was observed in only 62%
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39 of the cases, in agreement with previously reported data. It has been shown indeed that in some
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41 patients, pregnancy has a favourable effect on the natural history of pre-existing
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43 hyperprolactinaemia and a complete remission of the disorder has been reported in 17-37% of
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45 women after pregnancy.⁽²⁰⁾
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50 The follow-up investigations made in the children born from cabergoline-treated
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52 mothers indicated that *in utero* exposure to cabergoline did not influence their postnatal
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54 development. In particular, there was no evidence of an increased susceptibility to physical
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56 problems or of psychomotor or mental retardation in these children, observed up to the age of
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58 12 years. Further studies are however needed to confirm these findings.
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3 The limitations of our study are the retrospective character of the analysis and the
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5 limited number of included pregnancies, although this represents approximately one quarter of
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7 all previously reported cabergoline-induced pregnancies. In contrast, strengths of this report are
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9 the detailed information available for all pregnancies, including foetal exposure to cabergoline,
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11 the follow-up observation of the children and the inclusion of an age- and time-matched
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13 control group. This control group was blindly selected from the obstetrical register of our
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15 academic centre and included pregnancies in women considered at higher risk of obstetrical
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17 complications. We however excluded all patients referred for a known maternal or foetal
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19 complication. We however excluded all patients referred for a known maternal or foetal
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21 complication.
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25 In conclusion, our study shows no significant increase in the rates of spontaneous
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27 miscarriage, pregnancy or delivery complications, neonatal malformations or post-natal
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29 development abnormalities in the offspring of hyperprolactinaemic women treated with
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31 cabergoline at the time of conception. Further studies are still needed to confirm and extend
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33 these data.
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41 **Funding statement:**

42
43 This research did not receive any specific grant from any funding agency in the public,
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45 commercial or not-for-profit sector.
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For Peer Review

Figure legends

Figure 1. Schematic representation depicting the outcome of the 100 pregnancies initiated under cabergoline treatment and including 5 twin pregnancies (105 foetuses).

Figure 2. Individual variations in pituitary tumour height (mm) in the 37 women with an MRI performed before pregnancy and between the 24th and 32^d week of gestation. Tumor size before pregnancy is indicated by a close circle (●) and tumor size during pregnancy by the head of the arrow (▲). An increase of 2-8 mm was observed in 17 patients (46%). In 5 cases marked by an asterisk (*), cabergoline treatment had to be reintroduced during the third trimester for a symptomatic and/or visual-threatening increase of the adenoma. In 3 cases of macroprolactinomas (§), cabergoline had been continued during 20.5 weeks (case n° 37), 22 weeks (case n°36) or until delivery (case n°34).

m = microprolactinoma and M = macroprolactinoma at diagnosis.

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Table 1: Characteristics of pregnancies and deliveries in the cabergoline and control groups and in a regional register in Belgium

	Cabergoline group (n=100/84) [§]	Control group (n=163)	P value *	Flanders Registry 2003 (n =59,253)
Age of the mother (y)	31.8 ± 5.1	31.4 ± 4.9	NS	NA
Older than 35 (%)	22	21	NS	12
IVF (%)	20	7.9	P<0.05	4.1
Spontaneous miscarriage (%)	10	NA		NA
Hypertension/ Pre-eclampsy / eclampsy (%)	3 /1 /0	4.3 /1.2 /0.6	NS	4.8
Gestational diabetes (%)	4	3.7	NS	1.4
Multiple pregnancies (%)	5	5.5	NS	1.9
Foetal death [§] (%)	0	NA		0.47
Vaginal delivery (%)	77	70	NS	82
Assisted (% of vaginal)	8	21	P<0.025	10,7
Caesarean section (%)	23	30	NS	18
Preterm delivery (%)	9	19.6	P<0.025	7.4

* P values indicate significant differences between the cabergoline and the control groups

[§] Foetal death is defined as a death occurring between week 22 of gestation and delivery

[§] 100 pregnancies were leading to 84 deliveries in the cabergoline group

Table 2. Neonatal status in the cabergoline and control groups and in a regional register in Belgium.

	Cabergoline group (n=88)	Control group (n=173)	P value *	Flanders Registry 2003
Neonatal death ^{\$} (%)	0	5/173 (2.9%)		0.21
Post-natal death ^{\$} (%)	0	NA		0.68
Gender (% male)	46 (52%)	94 (54%)	NS	51.1
Birth weight < 2500g (%)	9/88 (10%)	29/173 (17%)	P<0.05	7.4
% IUGR	5/88 (5.6%)	9/173 (5.2%)	NS	NA
Neonatal intensive care (%)	5/88 (5.7%)	22/173 (12.7%)	P<0.05	4.4
Neonatal malformations	3/88 (3.4%)	11/173 (6.3%)	NS	1.6
Excluding chromosomal anomalies	3/88 (3.4%)	9/173 (5.2%)	NS	1.4

^{\$} Neonatal death is defined as a death occurring between the first and the 28th day of life. Post-natal death is defined as a death occurring between the 28th and 365th day of life.

* P values indicate significant differences between the cabergoline and the control groups.

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Table 3. Type of neonatal malformations diagnosed in the cabergoline and control groups

Malformations	Cabergoline group (§) n=88	Control group n=173
Chromosomal		Mucoviscidose (n=1) Angelman’s syndrome (n=1)
Neural	Congenital deafness (n=1)	
Cardiac		Intra-auricular communication (n=1)
Digestive		Laparoschisis and omphalocele (n=1) Important ombilical hernia (n=1)
Urinary	Unilateral hydronephrosis (n=1)	Unilateral renal agenesis (n=1)
Bone	Absence of right thumb (n=1)	Bilateral cleft lip and palate (n=1) Bilateral hip dysplasia (n=1)
Other		Absence of thyroid gland (n=1) Extended facial hemangioma (n=2)
Total	N = 3/88 (3.4%)	N = 11/173 (6.3%)

§ Foetal malformations leading to medical termination of pregnancy (n = 3 in the cabergoline group) are not included in this table, as they were not evaluable in the control group which contained only pregnancies continuing until delivery.

Figure 1

Figure 2