SAFETY AND EFFICACY OF CABERGOLINE ON PREGNANCY OUTCOME IN PATIENTS WITH MICROPROLACTINOMA

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ABSTRACT

BACKGROUND

Cabergoline (CAB) has emerged as an effective and well-tolerated drug for the treatment of hyperprolactinemia. However, the drug was included in the pregnancy risk category B by US Food and drug administration. There is limited literature evidence on the use of CAB for treating microprolactinoma during pregnancy, especially among Indian population. The present study was conducted to evaluate the pregnancy outcomes in patients with microprolactinoma, who underwent CAB treatment.

MATERIALS AND METHODS

The prospective study was conducted in a clinical practice setting in India from Jan 2016 to Dec 2017. The study included female subjects with microprolactinoma, aged between 20-35 years, treated with CAB (0.5 mg to 1.5 mg per week) for a period of 4-12 months, prior to conception and during early weeks of gestation. Level of prolactin was measured at diagnosis, pregnancy confirmation and at the 3rd month of gestation. Pregnancy, delivery and neonatal complications were the outcome measures considered. Statistical analysis involved descriptive analysis of the study variables.

RESULTS

The study included a total of 16 subjects with an average age of 26±3.15 years. The average level of prolactin decreased from 122.5±32 mcg/ltr. at diagnosis to 32 (28-54) mcg/ltr. at conception. Spontaneous abortion, pre-term delivery, and neonatal complications were observed in 37.5% (n=6) of the cases.

CONCLUSION

The current study findings corroborate the previous literature evidence suggesting CAB as an effective drug for the treatment of prolactinomas, specifically microprolactinoma. The study demonstrates that CAB administration, prior to conception and during early weeks of gestation, is not significantly associated with pregnancy-related complications.

KEYWORDS

Cabergoline, microprolactinoma, hyperprolactinemia, pregnancy outcomes.

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BACKGROUND

Cabergoline (CAB), a synthetic ergoline, is a potent inhibitor of prolactin secretion.[1] The drug was approved by the US Food and Drug Administration (FDA) on 23 December 1996 for the treatment of idiopathic or pituitary adenoma-related hyperprolactinaemic disorders.[2] Prolactinomas account for 45% of pituitary tumours and has an annual incidence of 6-10 cases per million population.[3-5] Microprolactinoma accounts for the majority of prolactinomas and are more prevalent among females, aged between 20-50 years, with a female-to-male ratio of 10:1.[6] The prevalence of hyperprolactinemia noted in women with secondary amenorrhea, galactorrhoea and both amenorrhea and galactorrhoea were 15–20%, 30%, and 75% respectively.[7,8]

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Over years, CAB has emerged as an effective and well-tolerated drug for the treatment of prolactinoma, outweighing bromocriptine, a commonly used ergoline derivative for the treatment of hyperprolactinemia.[9,10] However, bromocriptine is preferred over CAB due to the improved safety profile, in pregnancy.[11] Based on the limited experience of CAB in human pregnancies, the US FDA and the Australian Therapeutic Good Administration (TGA) have classified the drug into pregnancy risk category B and pregnancy risk category B1 respectively.[12] Animal-based studies have demonstrated the non-teratogenic effect of CAB.[13,14] However, human studies have demonstrated the association of CAB with risk factors such as spontaneous miscarriages, stillbirths, pre-term deliveries, congenital malformations and neonatal abnormalities.[15] Rains et al., based on a review, have reported the occurrence of ten congenital abnormalities among 199 human cases of CAB-associated pregnancy.[1]

Although certain studies have raised concern over the use of CAB as the first choice of drug in the treatment of prolactinoma-associated pregnancies, recent evidence suggests that the drug can be considered as the first choice in pregnant women. Bajwa et al. (2011) have suggested that

prolactinoma can be successfully treated with CAB during pregnancy without any adverse effects.[15] An observational, retrospective, multicenter study, involving 103 cases of pregnancy in 90 females undergoing CAB treatment, by Stalldecker et al. (2010) has reported that drug-related complications in pregnancy and in offspring exposed to CAB were comparable in patients undergoing treatment and normal population.[16] A long-term observational study by Colao et al. (2008), involving 380 cases of pregnancy, has shown that foetal exposure to CAB, during early period of gestation, does not increase the risk of miscarriage or foetal malformations.[17]

Several studies have entailed the necessity of further research to establish CAB as a better alternative for the treatment of prolactinoma during pregnancy.[15] In this regard, the present study has evaluated the pregnancy outcomes in patients with microprolactinoma, who conceived while undergoing CAB treatment.

MATERIALS AND METHODS

The prospective study involved female patients attending a clinical practice setting in India, from January 2016 to December 2017. Informed consent was obtained from all the participants. The study included female subjects with microprolactinoma, aged between 20-35 years, treated with CAB (0.5 mg to 1.5 mg per week) for a period of 4-12 months before conception and during early stages of pregnancy. The treatment was discontinued within three months of detection of pregnancy. Subjects with high blood pressure, pre-eclamptic toxaemia, history of psychosis and hepatic disease were excluded from the study.

Clinical and demographic details and drug history were obtained from all the subjects. Level of prolactin was measured at diagnosis, pregnancy confirmation, and at the 3rd month of gestation. The outcome measures considered were pregnancy, delivery and neonatal complications such as spontaneous abortions, preterm delivery, low birthweight and other complications (cleft lip) in neonates.

Statistics

Descriptive analysis was performed for the study variables. Data with normal distribution were represented as mean ± SD, without normal distribution as median (range), and categorical data as counts. All the statistical analyses were performed using MedCalc software version 14.8.1 (MedCalc software, Ostend, Belgium).

RESULTS

Among the 21 recruited subjects, five patients did not fulfil the inclusion criteria and were excluded from the study. The study considered a total of 16 subjects with an average age of 26 ± 3.15 years. The average duration between the initiation of treatment and detection of pregnancy was 6.8±1.12 months (Table 1). The average level of prolactin at diagnosis, detection of pregnancy and third month of pregnancy were 122.5 ± 32, 32(28-54) and 38(32-60) mcg/ltr respectively.

Complications related to pregnancy, delivery and neonate were noted in 37.5% (n=6) of the cases. Pre-term delivery and neonatal cleft lip was observed in the same case. All the subjects had normal thyroid profile and MRI of the subjects did not indicate changes in the size of the pituitary gland, after discontinuing the medication.

Factors	Value#
Age (years)	26.06 ± 3.15
Interval between date of diagnosis and pregnancy (months)	6.75 ± 1.12
Level of Prolactin (mcg/ltr.)	
At diagnosis	122.5 ± 32.12
At confirmation of pregnancy	32(28-54)
At third month of pregnancy	38(32-60)
Complications	
Present	6
Absent	10
Pregnancy Complication	
Spontaneous abortion	1
Delivery Complication	
Pre-term	4
Neonatal Complications	
Low birth weight	1
Cleft lip	1

Table 1. Descriptive Details of the Subjects

#Data with normal distribution are represented as mean ± SD, without normal distribution as median (range) and categorical data as counts.

DISCUSSION

Microprolactinomas are prolactin-secreting tumours in the pituitary gland with size <10 mm.[18] CAB is a well-tolerated and effective drug used in the treatment of prolactinomas.[19] CAB, the dopamine agonist, has shown to be effective in normalizing prolactin concentrations in 75-90% of the patients with microprolactinoma and tumor shrinkage by 72-92%.[20] Compared to macroprolactinoma, microprolactinoma shows faster response to CAB and significant improvement, following six months of treatment.[21] Studies have shown that dopamine agonist therapy can provide long-term remission in around 70% of the cases, after drug withdrawal.[22] In a retrospective study, involving 89 microprolactinoma patients, receiving either CAB or bromocriptine, Biswas et al. (2005) have demonstrated that the abrupt withdrawal of dopamine agonist, after 2-3 years of treatment provided long-term remission in 30-40% of the patients.[22]

Studies in mice models have demonstrated the non-teratogenic effects of CAB, at doses upto 8 mg/kg/day, during organogenesis. However, other studies have shown that a dose of 0.012 mg/kg/day increases the risk of post-implantation embryofoetal loss during organogenesis.[23] Several human-based studies have recommended the drug as the first choice of treatment for hyperprolactinemia in pregnant women due to its effectiveness and tolerability.[24-26] The study by Motazedian et al. (2017), on Swedish

population, has noted that subjects receiving CAB for hyperprolactinaemic infertility had significantly higher rates (82%) of pregnancy.[24] However, the non-teratogenic potential of CAB has not been clearly established.

Colao and colleagues (2008) conducted a 12-year observational study on Italian population and reported spontaneous miscarriages in 42%, stillbirths in 2%, and pre-term delivery in 18% of the patients undergoing CAB treatment. Neonatal abnormalities were noted in 9% of the infants. The study has concluded that foetal exposure to CAB is not linked to increase in miscarriage risk or foetal malformation.[17] A multicentre retrospective study, conducted on 90 Argentinian women with hyperprolactinemia, (2010) has evaluated the frequency of potential adverse effects in patients receiving CAB therapy at a dose of 0.125 to 5 mg/week for a period of 1 to 120 months, prior to detecting pregnancy.[16] The study evaluated 103 cases of pregnancies and the complications noted were as follows: spontaneous abortions (7.2%), pre-term delivery (8.8%), and low weight for gestational age (one case). Neonates born to mothers exposed to CAB in 3-25 weeks of gestation developed abnormalities such as Down syndrome (one case) and minor complications like umbilical and inguinal hernia. Two cases each of epilepsy and pervasive developmental disorder were noted in children. The study has concluded that the frequency of complications noted in pregnancies and/or offspring exposed to CAB and normal population was comparable.[16]

Similarly, Ricci et al. (2017) have collected information from 61 pregnancies of 50 women who were on CAB therapy. The study noted early termination in 19.7% and trisomy 18 in one neonate.[27] The study reported that comparison of the data with that of the general population revealed no significant increase in the frequency of spontaneous and induced abortions, and congenital malformations in subjects undergoing CAB treatment, prior to conception and early stages of gestation.

Literature review shows that there is no study evaluating the pregnancy outcomes associated with CAB therapy in Indian patients diagnosed with microprolactinoma, though there are some case reports on macroprolactinoma. Bajwa et al. (2011) have reported the case of a 27-year-old Indian female diagnosed with macroprolactinoma and treated successfully with CAB, throughout the gestational period, without marked increase in the adverse effects.[15] Similarly, Deepti Jain (2015) has reported the case of a 25-year-old patient with macroprolactinoma who was successfully treated with CAB after first trimester and delivered a healthy baby.[28]

Couture et al. (2014) have reported the case of a 37-year-old female patient presented with microprolactinoma during the 16th week of pregnancy and treated with CAB. The subject delivered a healthy baby and re-established the normal levels of prolactin within three months after delivery, without treatment.[29] The current study has noted complications associated with pregnancy in only 37.5% of the subjects who underwent CAB treatment at a dose of 0.5 to 1.5 mg per week for a period of 4-12 months, prior to pregnancy and followed up to three months of pregnancy. The study noted complications such as pre-term delivery (four cases), spontaneous abortion (one), and neonatal complications such as low birthweight and cleft lip (one case each).

The major limitations of the study include observational study pattern and very limited sample size. The study holds greater significance, as these is no literature evidence from India exploring the safety and efficacy of CAB in pregnant women diagnosed with microprolactinoma. Moreover, there is no clear consensus on the pregnancy outcomes associated with CAB in macro and microprolactinoma.

CONCLUSION

The current findings corroborate the previous studies indicating that CAB therapy during pregnancy does not increase the risk of potential adverse effect. Moreover, the study highlights the need to inform patients regarding the limited data available on the use of CAB during pregnancy.

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