The effect of celecoxib for treatment of preterm labor on fetuses during the second trimester of pregnancy: A pilot case series

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Original Article

The effect of celecoxib for treatment of preterm labor on fetuses during the second trimester of pregnancy: A pilot case series

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ABSTRACT

Objective: Although cyclooxygenase inhibitors effectively suppress uterine contraction, constriction of the fetal ductus arteriosus (DA) and oligohydramnios are major concerns. Celecoxib, a selective cyclooxygenase 2 inhibitor, is a potential potent tocolytic agent, but there are no studies that have evaluated the beneficial or adverse effects of celecoxib use on fetuses for more than 48 hours in pregnant women. We therefore aimed to evaluate the effect of middle-long-term celecoxib administration on the fetus during the second trimester of pregnancy, particularly in terms of fetal DA and amniotic fluid volume.

Materials and methods: We retrospectively extracted and reviewed data from patients with preterm labor who received celecoxib for tocolysis for more than 48 hours between 2016 and 2020. Celecoxib was used for tocolysis only when treatment of patients with conventional tocolytic agents was ineffective. Data on the peak systolic velocity in ductus arteriosus (PSV-DA) and the maximum vertical pocket (MVP) were collected.

Results: A total of 15 patients were eligible. The median gestational age at celecoxib introduction was 22.6 weeks, and the median period of administration was 9 days (range 3–40 days). The median gestational age at delivery was 27.1 weeks, and the median duration from initial celecoxib administration to delivery was 40 days. The Z scores of PSV-DA and MVP did not change significantly after celecoxib administration. During administration, PSV-DA exceeded the 95th percentile of the corresponding normal reference range in three cases, but the levels returned to normal after reduction or discontinuation of treatment. There was no oligohydramnios during the treatment.

Conclusion: Celecoxib administration for more than 48 hours in the second trimester of pregnancy might be safe and tolerable in terms of fetal PSV-DA and amniotic fluid volume as long as careful ultrasound monitoring is performed. Celecoxib could be an alternative for preterm labor when conventional tocolysis is not effective.

Introduction

Preterm birth, defined as birth before 37 weeks of gestation, generally affects 5 to 9% of pregnancies in developed countries, and the rates of preterm birth have increased in most industrialized countries [1]. It is one of the leading causes of neonatal death and accounts for approximately 15% of neonatal deaths [2]. Although most preterm babies survive, they are at an increased risk of short-term complications attributed to immaturity of multiple organ systems as well as neurodevelopmental disorders. In particular, preterm birth at less than 28 weeks of gestation is associated with an increased risk of neonatal complications, and the lower the gestational age at birth is, the higher the mortality rate will be [3].

Magnesium sulfate, ritodrine hydrochloride, and calcium channel blockers are first used to suppress uterine contractions during the second trimester of pregnancy, but if these drugs fail, cyclooxygenase (COX) inhibitors are considered for use for the period of time until the antenatal corticosteroid shows an effect. Historically, the nonselective COX inhibitor indomethacin has been used to inhibit uterine contractions and shown to significantly prevent preterm labor [4,5]. However, adverse effects on the fetus, including constriction of the ductus arteriosus (DA) and oligohydramnios, are concerns [6]. COX-2 is a key player in preterm labor

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[7], and it is hoped that celecoxib, a selective COX-2 inhibitor, will be as effective as indomethacin in the prevention of preterm labor and potentially prevent COX-1-specific fetal and maternal adverse effects. In fact, short-term (48 hours) use of celecoxib has been shown to be as effective as the use of indomethacin or magnesium sulfate, with no occurrence of constriction of DA [8–11]. However, there are no studies that have evaluated the benefits or adverse events of celecoxib use on fetuses in the middle-long term in pregnant women.

We therefore aimed to evaluate the effect of middle-long-term celecoxib administration (more than 48 hours) on the fetus during the second trimester of pregnancy, particularly in terms of fetal ductus arteriosus and amniotic fluid volume.

Materials and methods

We retrospectively extracted and reviewed patients with preterm labor who received celecoxib for tocolysis for more than 48 hours at Kyoto University Hospital between April 2016 and March 2020. In this study, celecoxib was used for tocolysis only when patients were extremely difficult to treat by conventional tocolytic agents, such as magnesium sulfate, calcium channel blockers and/or ritodrine. The administration of celecoxib was performed after the approval of the institutional review board on off-label drugs and obtaining written informed consent from patients. Basically, in most of hospitals in Japan, ritodrine is the first choice, followed by magnesium sulfate for preterm labor, and both tocolytic agents are used for relatively long time, with careful attention paid to their side effects. This may partly because the Japanese medical insurance system does not formally approve the use of calcium blockers for the treatment of preterm labor. However, in some institutes, including our own, calcium blockers are also used under hospital approval. The following patients were excluded: (1) those who received celecoxib for less than 48 hours, (2) those who desired termination of pregnancy at less than 22 weeks of gestation despite receiving celecoxib, and (3) those with multiple pregnancies.

Celecoxib was administered in following ways. The treatment period was limited to between 14 and 26 weeks of gestation. Patients were given a 100-mg celecoxib tablet orally every 12 hours. During treatment, fetal ultrasound examination was performed every day to assess the construction of DA and amniotic fluid volume. We evaluated the signs of DA construction using the peak systolic velocity in ductus arteriosus (PSV-DA) as an index based on a previous study: an increase in the flow velocity indicated a narrowing of DA [12,13]. The waveform of DA was obtained mainly from the longitudinal view at an insonation angle to a flow of <60 degrees. In principle, celecoxib was discontinued or reduced if PSV-DA exceeded the 95th percentile of the normal reference range [14]. Additionally, amniotic fluid volume was examined using the maximum vertical pocket (MVP) as an index. The discontinuation or reduction of celecoxib was considered if the MVP was less than 2 cm.

According to the electronic medical records of extracted patients, medical information such as the timing of the start and end of celecoxib administration, fetal PSV-DA, MVP of amniotic fluid, and outcomes of pregnancy were obtained and analyzed. The Z-scores of PSV-DA and MVP were obtained based on the normal reference range [14,15]. The data were presented as median (range). The Wilcoxon rank-sum test was used to compare the Z-scores of PSV-DA and MVP before and after celecoxib administration using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). A p-value of less than 0.05 was considered to be statistically significant.

This study was approved by the ethics committee of Kyoto University (R1895).

Results

During the study period, 22 patients received celecoxib for tocolysis. Seven patients were excluded for the following reasons: two for an administration period less than 48 hours, three for intention to terminate the pregnancy at less than 22 weeks of gestation despite receiving celecoxib, and two for twin pregnancies. Ultimately, 15 patients were included in the present study. The patient characteristics and pregnancy outcomes are shown in Table 1. The median patient age was 29 (25–36) years old, and nine (60.0%) patients were primigravida. The median gestational age at first use of celecoxib was 22.6 (15^{+4} -25^{+5}) weeks of gestation, and the median period of administration was nine (3–40) days. Eight cases (53.3%) were diagnosed with preterm premature rupture of fetal membranes (pPROM), so these patients were excluded from the calculation of MVP. Among the remaining 7 cases, there was no oligohydramnios (MVP <2 cm) during the administration. The babies' levels of serum creatinine were normal: 0.53 (0.30–0.66) mg/dL at birth, 0.39 (0.32–0.42) mg/dL at 1 month of age, and 0.22 (0.20–0.30) mg/dL at 3 months of age. The median gestational age at delivery was 27.1 (22^{+0} -37^{+3}) weeks, and the median duration from initial celecoxib administration to delivery was 40 (3–83) days. Nine babies (60.0%) were delivered by cesarean section. The rate of 1-minute Apgar scores below 5 was 66.7%, and that of 5-minute scores below 7 was 60.0%.

Fig. 1 shows the change in Z scores of PSV-DA (n = 15) and MVP (n = 7) based on the normal reference ranges [14,15] from the start date (before the administration) to the last date of administration of celecoxib. The Z scores did not change significantly after celecoxib administration compared to before celecoxib administration. The relationship between the duration of celecoxib administration and the Z score of maximum PSV-DA is shown in Fig. 2. There was no statistical correlation between the two, and long-term administration of celecoxib did not appear to cause elevated PSV-DA.

In 3 of 15 patients, celecoxib was reduced (case 15) or discontinued (cases 8 and 11) because PSV-DA exceeded the 95th percentile of the reference value. Fig. 3 shows the changes in PSV-DA in these three cases. In case 8, PSV-DA spiked 9 days after introducing celecoxib administration, and celecoxib was discontinued. In case 11, on the 6th day after the start of celecoxib administration, PSV-DA had risen slightly above the 95th percentile and then dropped spontaneously soon after. However, it increased again, and celecoxib treatment was ceased on the 17th day. In both cases, PSV-DA was decreased immediately after the medication was discontinued. In case 15, celecoxib administration was started at 17^{+3} weeks of gestation; at 22^{+4} weeks of gestation, on the 36th day, it was reduced to 50 mg/day due to an increase in PSV-DA. PSV-DA decreased soon after, and then, celecoxib was used until 23^{+0} weeks of gestation. Due to the prolonged period of celecoxib administration, PSV-DA continued to be measured thereafter, but PSV-DA did not increase again.

Discussion

In the present study, we found that celecoxib administration for more than 48 hours for the treatment of patients with preterm labor in the second trimester might be safe and tolerable in terms of fetal PSV-DA and amniotic fluid volume as long as careful ultrasound monitoring is performed. Indeed, increases in PSV-DA were observed in some cases; however, they were reversible and decreased to the normal range soon after celecoxib cessation. This is the first pilot case series to evaluate the effects of celecoxib administration for more than 48 hours during the second trimester on the fetus in the context of fetal ductus arteriosus and amniotic fluid volume.

Table 1
Patients' characteristics, administration durations, adverse effects and pregnancy outcomes.

Case	Age	Parity	Gestational age at Celecoxib introduction	Gestational age at Celecoxib cessation	Reason for Celecoxib cessation	Administration duration (days)	>95 percentiles in PSV-DA	<2 cm in MVP	Gestational age at delivery	Period from initial administration to delivery (days)	Mode of delivery	BW (g)	Apgar (1 min/ 5 min)
1	29	P	23w6d	24w1d	Failure	3	–	N/A[b]	24w1d	3	CS	491	6/8
2	35	M	22w4d	22w6d	Relieved	3	–	–	26w6d	30	CS	1050	3/7
3	30	M	23w2d	23w5d	Relieved	4	–	N/A[b]	27w1d	27	VD	890	2/6
4	36	M	24w4d	25w2d	Relieved	6	–	–	30w3d	41	CS	1660	5/8
5	28	P	15w4d	16w3d	Relieved	7	–	N/A[b]	22w0d	45	VD	365	1/1
6	36	P	25w5d	26w4d	Relieved	7	–	–	37w3d	82	VD	3104	9/9
7	31	P	23w3d	24w3d	Relieved	8	–	N/A[b]	33w2d	69	VD	1880	8/9
8	28	P	21w4d	22w5d[a]	Elevation	9	+	–	32w2d	75	VD	1946	8/9
9	29	M	24w0d	25w4d	Failure	12	–	N/A[b]	25w5d	12	CS	716	1/5
10	29	P	22w4d	24w2d	Relieved	13	–	–	34w3d	83	CS	2150	3/8
11	25	M	18w3d	20w4d[a]	Elevation	16	+	–	24w1d	40	CS	626	6/7
12	30	P	23w2d	25w4d	Relieved	17	–	N/A[b]	27w0d	26	CS[c]	839	1/6
13	29	P	22w0d	25w1d	Failure	23	–	N/A[b]	25w2d	23	CS	684	2/5
14	33	M	22w3d	27w0d	Relieved	33	–	N/A[b]	27w5d	37	CS	1140	1/7
15	26	P	17w3d	23w0d[a]	Elevation	40	+	–	27w4d	71	VD	892	5/6

PSV-DA: peak systolic velocity in ductus arteriosus, MVP: maximum vertical pocket, BW: fetal body weight, P: primigravida, multigravida, Failure: labor developed despite celecoxib administration, Relieved: Uterine contraction was relieved. Elevation: PSV-DA was elevated. N/A: not applicable, CS: cesarean section, VD: vaginal delivery.
[a] Celecoxib was reduced or discontinued because PSV-DA was elevated in these cases.
[b] MVP was not used for evaluation because preterm premature rupture of fetal membranes was obvious in these cases.
[c] CS was performed under general anesthesia.

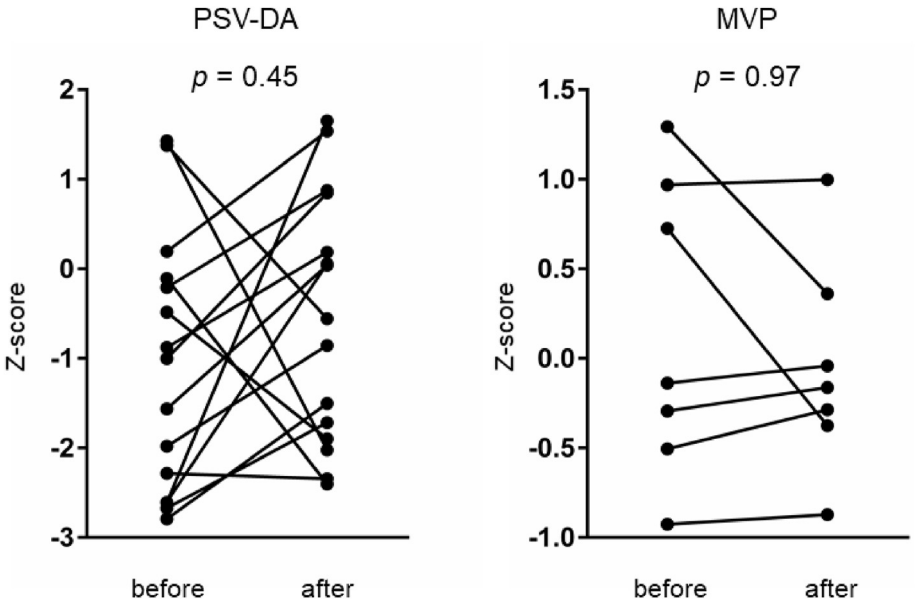

Fig. 1. The change in Z-scores of PSV-DA (n = 15, left panel) and MVP (n = 7, right panel) based on the normal reference range from the start date (before the administration) to the last date of administration of celecoxib.

The selective COX-2 inhibitor celecoxib has real value when conventional tocolytic agents are ineffective against preterm labor in the second trimester. To prevent preterm birth and obtain uterine quiescence, it is essential to suppress prostaglandin production, which induces cervical ripening and uterine contractions, thereby leading to preterm labor [7]. Therefore, it is very reasonable to inhibit COX-2 when existing tocolytic agents are not working. It has been suggested that COX-2 rather than COX-1 is involved in the production of preterm prostaglandins [16,17], and the selective COX-2 inhibitor, celecoxib is thought to be as effective as a nonselective COX inhibitor. However, COX inhibitors are known to cause DA constriction due to inhibition of the dilator effects of prostaglandins [18,19] and decreased amniotic fluid production due to decreased fetal renal blood flow [20–22]. There are few reports of celecoxib use during pregnancy, and its safety needs to be evaluated. According to a few previous studies, celecoxib inhibits preterm labor in humans, with no contraction of DA and less reduction in amniotic fluid volume than indomethacin use; however, all of these studies involve short-term use within 48 hours [8,10,11]. Our present pilot study is the first to evaluate the effect of celecoxib use for more than 48 hours on DA and amniotic fluid volume during pregnancy.

Celecoxib may have less impact on the fetal ductus arteriosus than nonselective COX inhibitors. The patency of DA is secured by prostaglandins, which increase intracellular cAMP concentrations, thereby inhibiting the sensitivity of ductus contractile proteins to calcium. It has been reported that DA is exposed to both locally released and circulating prostaglandins and that the latter are

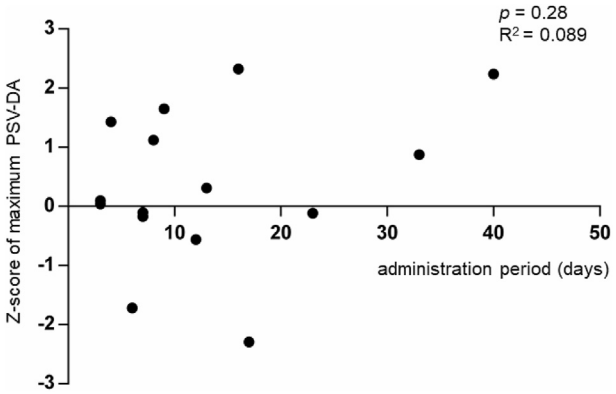

Fig. 2. The relationship between the duration of celecoxib administration and the Z-score of maximum PSV-DA.

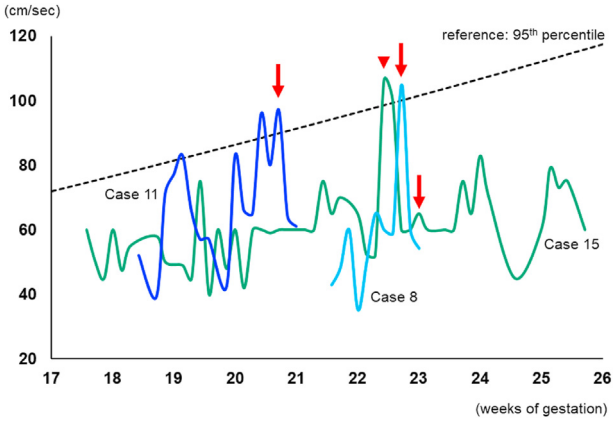

Fig. 3. The changes in PSV-DA in three cases whose PSV-DA exceeded the 95th percentile of the corresponding normal reference range. Arrows indicate the timing of discontinuation of celecoxib. The arrowhead indicates the timing of celecoxib reduction.

primarily responsible for maintaining ductal patency in utero [23]. The major sources of circulating prostaglandin E2 in the fetus are considered to be the placenta, especially the chorion, and fetal membranes. Intriguingly, the expression of COX-2 in the chorion and fetal membranes increases with advancing gestation until 28 weeks of gestation [24,25]. Conversely, COX-2 expression in the second trimester is relatively low, indicating that the adverse effect of celecoxib may be minimized.

Oligohydramnios is another nonnegligible adverse effect of using COX inhibitors during pregnancy [20,21], although a decrease in amniotic volume did not occur in our cases. Prostaglandins participate in processes of renal circulation, including vasodilatation, renin secretion, and sodium and water excretion. If vasoconstrictive forces stimulated to maintain the filtration fraction are not balanced by prostaglandin-induced vasodilatation, renal failure may occur [26]. It is assumed that COX inhibitor-induced renal injury in the fetus and oligohydramnios may be caused by similar pathophysiologic mechanisms. Stika CS et al. [8] showed that both nonselective COX inhibitors and selective COX-2 inhibitors were associated with a decrease in amniotic fluid volume, with a greater effect by nonselective COX inhibitors. These results suggest that both isoforms of COX affect fetal renal circulation and that COX-2 selectivity may alleviate the decrease in amniotic fluid volume.

Careful ultrasound monitoring of PSV-DA and MVP on a daily basis is essential when administering celecoxib to patients with preterm labor during the second trimester. It is currently unknown whether the likelihood of adverse effects of celecoxib on the fetus is related to the cumulative number of days of treatment, even though they seemed to be unrelated in the present study. Whether there is a specific gestational week in which DA is susceptible to being affected by celecoxib is also unclear in the current pilot study. In our three cases in which PSV-DA exceeded the 95th percentile of the reference value, PSV-DA rose sharply without any warning but declined rapidly with withdrawal of celecoxib. This finding suggests the importance of daily monitoring and immediate drug suspension if any abnormalities, including a decrease in amniotic fluid volume, occur.

When administering celecoxib for a long period of time, its adverse effects on the mother is also a concern. The large randomized controlled trial showed that celecoxib, at moderate doses, was noninferior to ibuprofen or naproxen in terms of cardiovascular safety [27]. This trial also revealed that the renal events risk of celecoxib was lower compared with ibuprofen, but was not significantly lower compared with naproxen. Nevertheless, these maternal risks associated with long-term administration of celecoxib cannot be overlooked. Consideration the effects on the fetus as well, in principle, celecoxib administration should be limited to as short a period as possible.

The current study has some limitations. This is a retrospective pilot case series, and the sample size was small. In addition, this study was not designed to evaluate the effect of celecoxib on prolongation of the gestational period. It should be noted, however, that celecoxib ameliorated uterine contraction for more than one week in 11 (73%) patients, even though treatment of all patients with conventional tocolytic agents was difficult. Furthermore, the length of gestation extension in our case series was 40 (3–83) days, which was longer than that of indomethacin (22.9 days) [28]. More prospective studies with larger sample sizes are needed to assess the efficacy and safety of celecoxib for preterm labor.

Conclusion

During the second trimester, celecoxib administration for more than 48 hours can cause an increase in PSV-DA and a decrease in amniotic fluid volume. However, these adverse effects on the fetus can be detected easily by careful daily ultrasound monitoring, and the change is reversible by appropriate withdrawal of the drug.

Funding

None.

Ethics statement

This study did not use the human or animal samples. All the procedures were followed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all the patients to be included in the study.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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