J Anesth (2014) 28:911–918
DOI 10.1007/s00540-014-1830-x

ORIGINAL ARTICLE

Effect of propofol on prostaglandin E_2 production and prostaglandin synthase-2 and cyclooxygenase-2 expressions in amniotic membrane cells

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Received: 15 October 2013 / Accepted: 30 March 2014 / Published online: 22 April 2014
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Abstract
Purpose Surgery during pregnancy can be a cause of preterm labor or birth, possibly resulting from anesthetic agents or direct effects of surgery. This study was aimed to investigate the effect of propofol on uterine contractility by examining prostaglandin E_2 (PGE_2) production and the expression of PGE synthase 2 (PGES2) and cyclooxygenase-2 (COX-2) in amniotic membrane cells.
Methods Amniotic membranes were collected from healthy full-term women who underwent cesarean section at 37–40 weeks of gestation. The amniotic cells were cultured in α-modified-Eagle's medium with 10 % fetal bovine serum for 24 h at 5 % CO_2 in a 37 °C incubator. Then, various doses of propofol (0.01–10 μg/ml) were used for treatment for 3 h. PGE_2 concentrations in conditioned media were evaluated using ELISA. PGES2 and COX-2 expression were examined using RT-PCR and Western blot. Cell viability and apoptosis were examined by MTT, ATP assays, and the TUNEL method.
Results PGE_2 production significantly decreased at 0.1 and 1.0 μg/ml propofol concentrations compared to controls. COX-2 and PGES2 mRNA expression was decreased in a dose-dependent manner with a significant difference at 0.1 μg/ml propofol compared to controls. The protein expression of COX-2 showed a similar result to mRNA expression, but protein expression of PGES2 was not significantly decreased. No effect of propofol was found in cell viability.
Conclusions This study showed that propofol reduced the production of PGE_2 and the expression of COX-2 and PGES2 without affecting cell viability.

Keywords Propofol · Uterine contractility · Prostaglandin E_2 · Prostaglandin E synthase 2 · Cyclooxygenase-2

Spontaneous preterm birth, defined as delivery weeks of gestation, occurs as an obstetrical complication in 5 % to 11 % of all births and results in 70–80 % of neonatal mortality [1].

The incidences of preterm labor or preterm birth are significantly increased in pregnant women undergoing nonobstetrical abdominal surgery during the third trimester compared to those who undergo surgery during the first or second trimester [2]. Mazze and Kallen [3] reported in a registry study of 5,405 cases that the incidence of premature birth was increased by 46 % in women undergoing nonobstetrical surgery during pregnancy (7.47 %) when compared to a control rate of 5.13 %. The cause for increased risk of preterm birth after surgery during pregnancy was not clearly determined, but three possibilities can be considered: one is infection and/or inflammation associated with underlying disease or the surgery [4], the second is direct adverse effects from the surgery [5], and the third possible cause is the type of anesthesia agent or method of anesthesia. Therefore, it has been thought that it is very important relative to the safety of pregnant women

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or the fetus to use or develop anesthesia agents without adverse effects such as premature labor or birth for surgery during pregnancy.

The onset of labor is caused by the activation of numerous inflammatory mediators. Prostaglandins (PGs) are a class of small lipid inflammatory mediators involved in various processes such as platelet aggregation, release of neurotransmitters, or the regulation of immune function. PGs produced by the maternal deciduas and fetal amnion are primarily important in the initiation and maintenance of labor in women by contributing to increased uterine contractility and cervical remodeling [6, 7]. The concentrations of PG and PG synthase were increased in myometrium and deciduas and the amniotic fluid at the onset of labor [8–10]. PGs soften the uterine cervix [11] and stimulate uterine contractions [12]. In addition, PGs result in rupture of the amniotic membrane by inducing remodeling of extracellular proteins and apoptosis [13]. Administration of exogenous PG induces uterine contraction [14], whereas selective PG synthesis inhibitor blocks the production of PG, delays the delivery, and extends the pregnancy [15, 16]. These results suggest that PG plays an important role in the onset of labor and throughout delivery.

Among PGs, prostaglandin E_2 (PGE_2) is well studied and has been known as an important labor-inducing factor. In preterm births, the concentration of PGE_2 in the amnion increases during the onset of labor compared to before labor [17]. PGE_2 is converted from PGH_2 by PGE synthase (PGES) and PGH2 is synthesized from arachidonic acid (AA) by cyclooxygenase-2 (COX-2). PGES has three subtypes of cytoplasmic PGES (cPGES), microsomal PGES (mPGES)-1, and mPGES-2. PGES regulates the synthesis of PGE_2, selectively coupled with COX-1 and COX-2 depending on each subtype [18, 19]. Recently, Astle et al. [20] found that the expressions of COX-2 and mPGES-2 were significantly increased in lower segment myometrium during term labor.

Propofol (2,6-diisopropylphenol) has a short half-life and rapidly degrades in the circulatory system; it is a widely used intravenous anesthetic agent. It has been safely used for not only cesarean section but also for nonobstetrical operations or procedures during pregnancy [21, 22]. It has recently been shown that propofol also has nonanesthetic effects, including antioxidant or antiinflammatory effects [23]. In particular, propofol may suppress PGE_2 synthesis in human mononuclear cell lines and peripheral mononuclear cells [24, 25]. However, there are no reports on the effect of propofol on the production of PGE2 and the expression of PGES2 and COX-2.

Therefore, we hypothesized that propofol has a beneficial effect on the prevention of preterm labor or birth if it inhibits PGE_2 synthesis of amnion cells. This study examined the effect of propofol on the production of PGE_2 and the expression of PGES-2 and COX-2 in human amniotic membrane cells.

Materials and methods

This study was approved by the Institutional Review Board of Pusan National University Hospital. All women who participated in the study gave written informed consent.

Isolation and culture of human amniotic membranes

Human amniotic membranes were obtained from ten healthy full term women (ASA I) undergoing elective cesarean section at 37–40 weeks of gestation. The amniotic membrane tissues were separated from the chorion within at least 1 h after delivery by blunt dissection and were rinsed with phosphate-buffered saline (PBS).

The peeled amniotic membranes were treated with 0.25 % trypsin (Gibco BRL, Grand Island, NY, USA) for 20 min before mechanical mincing. Then, the pieces of amniotic membranes ($\sim 5 \times 5$ mm^2) were incubated at 37 °C in Dulbecco's phosphate-buffered saline (DPBS; Gibco BRL) containing 2 mg/ml collagenase type II (Gibco BRL) for 1 h. Then, the digested tissues were passed through a 40-μm cell strainer (BD Biosciences, Bedford, MA, USA) to remove larger fibrous tissue remnants.

The dispersed cells were harvested and cultured in modified Eagle's medium-α (MEM-α; Gibco BRL) containing 1 % penicillin/streptomycin (Gibco BRL) and 10 % fetal bovine serum (FBS; Gibco BRL) under 5 % CO_2 at 37 °C. Seven days later, nonadherent cells were removed and the culture was continued, replacing the medium twice a week.

Propofol treatment

This study used a commercially available propofol (DongKuk Pharm., Seoul, Korea), which is made up of 1 % propofol, 10 % soybean oil, 1.2 % purified egg phospholipid, 2.25 % glycerol, and sodium hydroxide to adjust the pH. It was diluted with culture medium and added to cell cultures at various concentrations (0.01–10 μg/ml) for 3 h.

Prostaglandin E_2 (PGE_2) assay

Amniotic membrane cells (2×10^5/well) were seeded in 6-well plates and cultured for 24 h in a 37 °C, 5 % CO_2 incubator. Then, propofol was added to the culture at concentrations ranging from 0.01 to 10 μg/ml for 3 h. PGE_2 levels were measured in conditioned medium from cell cultures by using the Correlate-EIA high-sensitivity

prostaglandin E_2 enzyme immunoassay kit (Enzo Life Sciences, Plymouth Meeting, PA, USA) according to the manufacturer's instructions. Each determination was made in quintuplicate.

MTT assay

The cells (1×10^5/well) were seeded in 24-well plates and cultured for 24 h at 37 °C in a 5 % CO_2 incubator. Then, cells were exposed to propofol (0.01–10 μg/ml) for 3 h. After treatment of propofol, the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; Sigma, St. Louis, MO, USA] assay was performed by adding 100 μl MTT solution (5 mg/ml in PBS at pH 7.2) into each well and incubating at 37 °C. After 1 h, the medium was removed and 100 μl dimethyl sulfoxide (DMSO; Sigma) was added into each well. The plate was gently rotated on an orbital shaker for 10 min to completely dissolve the precipitate. The absorbance was detected at 540 nm with a microplate ELISA Reader (Spectra MAX 250; Molecular Devices, Sunnyvale, CA, USA). All experiments were repeated three times.

ATP assay

After the cells (1×10^5/well) were treated with propofol for 3 h, ATP was measured with an ATP Bioluminescence Assay kit (Roche Applied Science, Indianapolis, IN, USA) following the manufacturer's instructions. Briefly, the medium was aspirated and the cell pellets were extracted by boiling 100 mM Tris (tris(hydroxymethyl) aminomethane) buffer containing 4 mM EDTA (ethylenediaminetetraacetic acid) for 2 min to inactivate NTPases. Cell remnants were removed by centrifugation at 1,000 *g*. Supernatants were removed and placed on ice. Determination of free ATP was as outlined in the manufacturer's protocol. Light emission was measured at 562 nm using a luminometer. ATP levels were normalized to protein content as measured by the Bradford assay (Bio-Rad, Hercules, CA, USA).

TUNEL assay

The TdT-mediated dUTP nick-end labeling (TUNEL) assay was performed using a DeadEnd Fluorometric TUNEL System (Promega, Madison, WI, USA). Briefly, the human amnion membrane cells were grown on 60-mm dishes and treated with propofol for 3 h as previously described. Cells were first washed in equilibration buffer, incubated with TdT enzyme in a humidified chamber at 37 °C for 1 h, washed, and then incubated at room temperature for 30 min in the dark with fluorescein-conjugated anti-digoxigenin. The washed specimens were counterstained with propidium iodide (1 μg/ml) and visualized with a fluorescent microscope.

RNA preparation and RT-PCR

Total RNA was extracted using the Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. Complementary DNA (cDNA) was synthesized from 2 μg total RNA with M-MLV Reverse Transcriptase (ELPIS-Biotech, Daejon, Korea) using a random hexamer (Bioneer, Daejon, Korea) at 42 °C for 1 h. Template cDNA was subjected to polymerase chain reaction (PCR) amplification using gene-specific sense and antisense primers under the following conditions: 28–35 cycles of denaturation at 95 °C for 30 s, annealing at 57 °C for 30 s, and extension at 72 °C for 30 s in a thermal cycle. The primers of each gene were as follows: sense 5′-TGA AGGCTGTGAACGAGCAG-3′ and antisense 5′-CATTG GGGGAGATCAGGTGC-3′ for PGES2; sense 5′-CCTT CCTCCTGTGC CTGATG-3′ and antisense 5′-CTGGCC TCGCTTATGATCT-3′ for COX-2; and sense 5′-GAC TACC TCATGAAGATC-3′ and antisense 5′-GATCCAC ATCTGCGGAA-3′ for β-actin. Beta-actin expression was used as a control. The PCR products were visualized by electrophoresis on 1.5 % agarose gel. The PCR bands were quantified and normalized relative to the control band with the National Institutes of Health (NIH) Image program (Image-J 1.35d; NIH, Bethesda, MD, USA).

Western blot analysis

Cells were extracted by homogenization in the presence of ice-cold lysis buffer [50 mM Tris–HCl (pH 7.5), 150 mM NaCl, 1 % Nonidet P-40, and 1 mM EDTA] containing protease inhibitor. The protein content of the cell lysate was determined with Bradford reagent (Bio-Rad) using bovine serum albumin (BSA) as the standard. Forty micrograms of protein were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene fluoride (PVDF) membrane (Millipore, Bedford, MA, USA).

The membrane was incubated with anti-human PGES2 rabbit IgG antibody (1:1,000; ProteinTech Group, Chicago, IL, USA) and anti-human COX-2 goat IgG antibody (1:1,000; Santa Cruz Biotechnology, Santa Cruz, CA, USA) for 1 and 2 h, respectively, at room temperature in TBS containing 0.1 % Tween-20 (TBST) supplemented with 5 % nonfat dry milk. Then, the membrane was incubated with anti-actin rabbit IgG antibody (1:5,000; Sigma) for 1 h at room temperature. After washing three times with TBS-T, the blotted membranes were incubated with horseradish peroxidase (HRP)-conjugated goat antibody (Santa Cruz Biotechnology) for 30 min at room

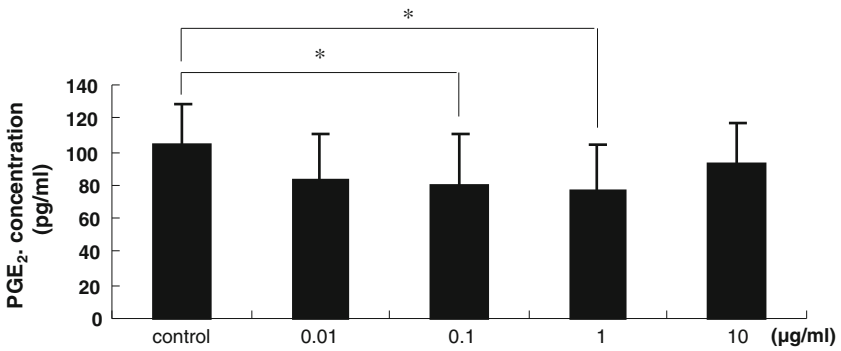

Fig. 1 Prostaglandin E_2 (PGE_2) concentrations in conditioned medium treated with various concentrations of propofol. Cells were cultured in media treated with propofol (0.01–10 μg/ml) or without (control) for 3 h. Conditioned media were collected and concentrations of PGE_2 assayed by ELISA. Data are presented as mean ± SD of independent experiments for ten amnion samples. $^*P < 0.05$

temperature. After washing three times with TBS-T, the protein bands were visualized using an enhanced chemiluminescence (ECL) detection system according to the recommended procedure (Amersham Pharmacia Biotech, Piscataway, NJ, USA). Actin expression was used as the control. The protein bands were quantified and normalized relative to the control band with NIH Image program (Image-J 1.35d).

Statistical analysis

Statistical analysis was performed with one-way analysis of variance (ANOVA), followed by Scheffe's F test for multiple comparisons using SPSS (version 12.0) program. $P < 0.05$ was considered to be statistically significant.

Results

Effects of propofol on PGE_2 synthesis

PGE_2 synthesis began to decrease from a propofol concentration of 0.01 μg/ml and significantly decreased at propofol concentrations of 0.1 μg/ml and 1.0 μg/ml compared to the controls. However, there was no significant difference in PGE_2 synthesis between the 10 μg/ml concentration of propofol and the control group (Fig. 1).

Effects of propofol on the expression of COX-2 and PGES2

Propofol treatment resulted in a decrease in the expression of PGES2 and COX-2 mRNA transcripts. Especially, the expression of these two factors was significantly decreased from 0.01 μg/ml propofol compared to controls (Fig. 2). Protein expressions of these two factors were also decreased by propofol treatment. However, the expression of PGES2 was decreased at all concentrations of propofol without

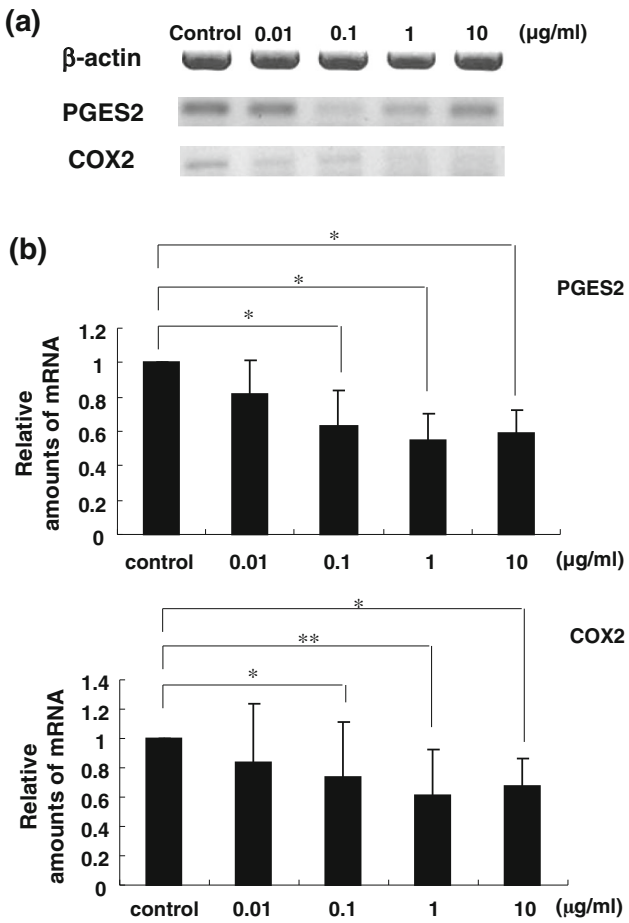

Fig. 2 Expressions of PGES2 and COX-2 mRNA transcripts. Amniotic cells were cultured in media treated with propofol (0.01–10 μg/ml) or without (control) for 3 h. **a** After propofol treatment, mRNA expression of PGES2 and COX-2 was analyzed by RT-PCR. **b** Densitometry analysis of expressed PGES2 and COX-2 content was performed using Image J (NIH Image Soft, version 1.35d) and normalized by β-actin level. Data are presented as mean ± SD of independent experiments for ten amnion samples. $^*P < 0.05$, $^{**}P < 0.01$

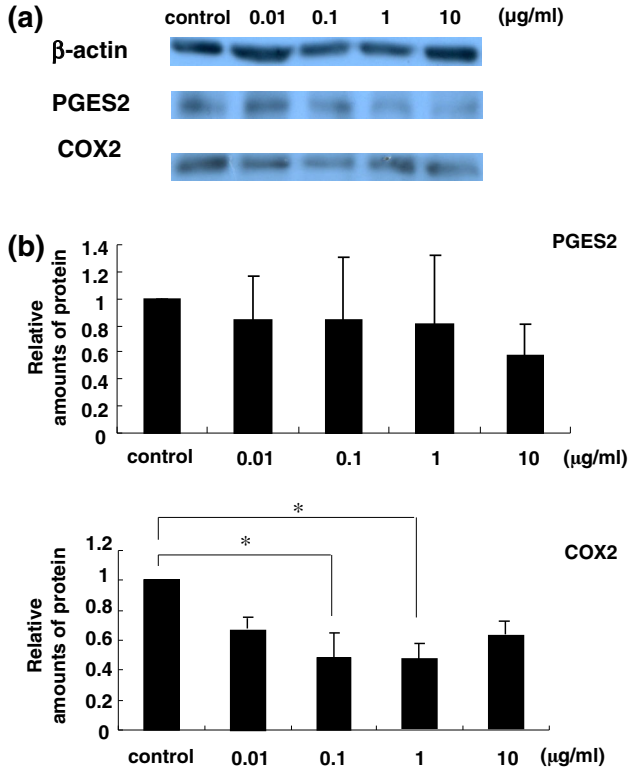

Fig. 3 Expressions of PGES2 and COX-2 proteins. Amniotic cells were cultured in media treated with propofol (0.01–10 μg/ml) or without (control) for 3 h. **a** Immunoblot with anti-PGES2 and anti-COX-2 antibody. **b** Densitometry analysis of expressed PGES2 and COX-2 content was performed using Image J (NIH Image Soft, version 1.35d) and normalized by control level. Data are presented as mean ± SD of independent experiments for ten amnion samples. $^*P < 0.05$

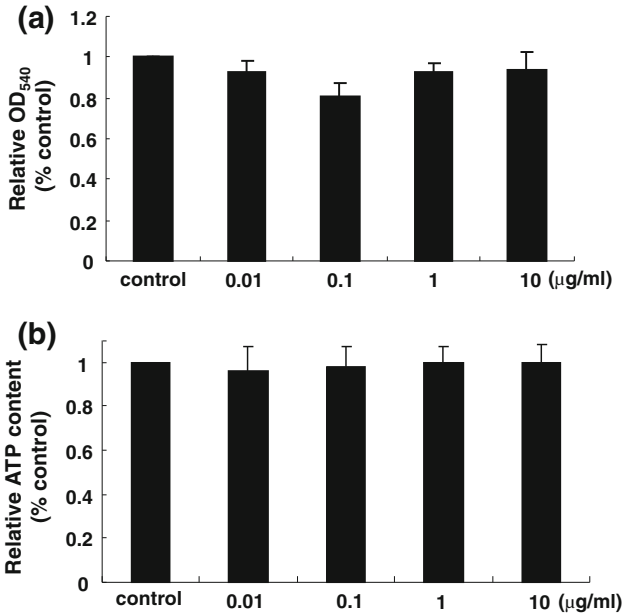

Fig. 4 Cell viability by MTT assay (**a**) and ATP assay (**b**). Amniotic cells were cultured in media treated with propofol (0.01–10 μg/ml) or without (control) for 3 h. Data are presented as mean ± SD of independent experiments for ten amnion samples

significant differences compared to the control group, whereas the expression of COX-2 showed a significant decrease at 0.1 and 1.0 μg/ml propofol concentrations (Fig. 3).

Effects of propofol on cell proliferation and apoptosis of amniotic membrane cells

The effect of propofol on cell viability of the amniotic membrane was examined by MTT and ATP assays. Cell proliferation and cellular ATP content were not affected by propofol treatment regardless of treatment concentrations (Fig. 4). However, cell apoptosis was not detected at propofol concentrations less than 1 μg/ml, but it began to be detected at high propofol concentrations of 10 μg/ml (Fig. 5).

Discussion

This study shows that propofol inhibited the production of PGE_2 and the expression of COX-2 and PGES2 in human amniotic membranes without affecting cell viability. This result is consistent with other recent studies, showing that propofol inhibited PGE_2 synthesis by directly reducing the expression of COX in immune cells of humans as well as murine immune cells [24, 26]. Considering that PG plays an important role in the onset of labor and throughout delivery [13], this result suggests that propofol may reduce uterine contraction by inhibiting PG synthesis.

A notable finding in the present study was that propofol also inhibited the expression of PGES2. This result suggests that propofol can reduce PGE_2 synthesis by reducing the expression of PGES2 and COX-2. However, two enzymes, COX-2 and PGES2, showed a different pattern in their mRNA transcripts and protein expressions. Expressions of both COX-2 mRNA and protein significantly decreased at 0.1 and 1 μg/ml concentrations, whereas mRNA expression of PGES2 was significantly decreased compared to controls, but protein expression of PGES2 was decreased without significant differences. The expression pattern of COX-2 was the same as that of PGE_2 synthesis. This result suggests that the rate-limiting step in PGE_2 synthesis is the conversion of AA to PGH_2 by COX-2 rather than the conversion of PGH_2 to PGE_2 by PGES2. Meadows et al. [27] reported that there is no evidence to suggest the conversion step of PGH_2 to PGE_2 has a rate-limiting or regulated step in terms of PG synthesis in human fetal membranes.

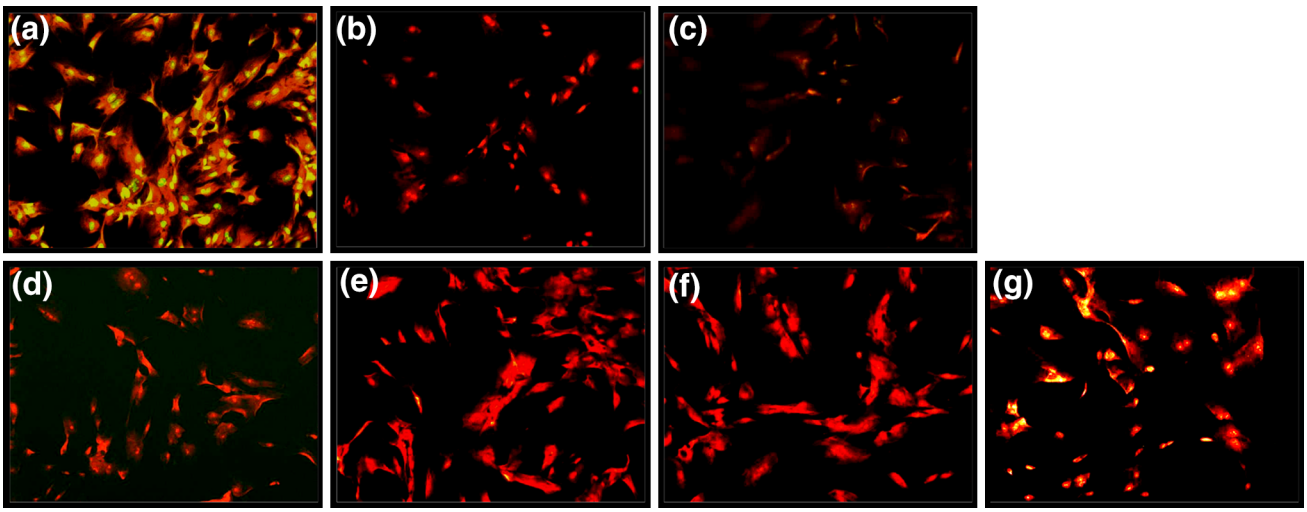

Fig. 5 Apoptosis assay by TUNEL method. Amniotic cells were cultured in media treated with propofol (0.01–10 μg/ml) for 3 h: positive control (**a**), negative control (**b**), control (**c**), 0.01 μg/ml (**d**), 0.1 μg/ml (**e**), and 1 μg/ml (**f**) and 10 μg/ml (**g**) propofol concentrations. Apoptosis of amniotic cells was detected at the high dose of 10 μg/ml propofol. ×200

The present study showed that propofol did not affect the viability of human amniotic membrane cells at concentrations ranging from 0.01 to 1 μg/ml. Thus, the decreased PGE_2 synthesis and expression of PGES2 and COX-2 shown in the present study are not attributable to cell toxicity by propofol. It was previously reported that propofol also did not affected the viability of murine immune cells [24]. These results support that propofol may be a safe anesthesia agent without affecting cell viability.

However, an unusual finding in the present study was that PGE_2 production and COX-2 expression were decreased at 0.1 and 1 μg/ml propofol concentrations, but increased again at 10 μg/ml, which concentration induced cell apoptosis. The reason for the higher PGE2 production at 10 μg/ml propofol compared to that at 0.1 and 1 μg/ml may be considered in two aspects. One is that propofol may have a peak concentration in its effect on PGE2 synthesis. In this respect, our result shows that the inhibitory effect of propofol on PGE2 synthesis may peak at the 1 μg/ml concentration. The other possible reason is that 10 μg/ml propofol begins to induce cell apoptosis and the effect of propofol on PGE2 synthesis may thus disappear. Therefore, these results meant that when propofol is used for nonobstetrical surgery during pregnancy, it should be used at an appropriate concentration that does not induce an increase of uterine contractions and cell apoptosis.

Luo et al. [28] reported in their experiment to examine the effect of propofol on the apoptosis of human umbilical vein endothelial cells (HUVECs) that cell apoptosis was not found at 5 μM propofol and that cell apoptosis induced by tumor necrosis factor (TNF)-α was also inhibited by the treatment with propofol ranging from 12.5 to 100 μM. This result indicates that propofol may rather reduce than stimulate cell apoptosis. However, this finding differs from our present result, which showed that cell apoptosis was found at propofol concentrations of 1 μg/ml (5.6 μM) or less but was not found at 10 μg/ml (56 μM).

It has been reported that the plasma concentration of propofol during the induction of anesthesia in humans is up to 30 μM, and burst suppression doses of propofol for cerebral protection are up to 60 μM [29, 30]. Therefore, the 100 μM dose used by Luo et al. [28] is very high, above physiological levels. It is unexpected that this dose inhibits apoptosis of HUVECs. When mouse oocytes were exposed to in vitro maturation under the treatment of propofol ranging from 0.01 to 10 μg/ml concentrations, the rate of in vitro maturation was significantly decreased only at the 10 μg/ml propofol concentration [31]. This result means that propofol at supraphysiological concentrations could harm cell viability and function. Our present study chose propofol concentrations ranging from 0.01 to 10 μg/ml, considering the results of Alsalili et al. [31]. Nevertheless, further study is needed to determine an appropriate concentration of propofol that does not affect cell viability. Another cause of the different results between the study of Luo et al. [28] and our study may be that a different cell type used because each cell type has a different sensitivity to propofol and response to PGE_2.

The PGE_2 concentration is increased in amniotic membranes derived from term labor or preterm birth compared to that without labor [8, 9, 17], implying that the condition of amniotic membrane can affect the concentration of PGE_2. However, in our present study two reasons may preclude the possibility that PGE_2 concentration was influenced by the condition of the amniotic membranes provided. First, the amniotic membrane tissues were

obtained from healthy full-term women (ASA I) undergoing elective cesarean section at 37–40 weeks of gestation. Second, the activity of PGE_2 synthesis-related enzymes was assayed not in obtained fresh tissues but in cultured in vitro cells for 7 days.

In conclusion, the present study shows that propofol inhibited the production of PGE_2 and the expression of COX-2 and PGES2 without affecting cell viability at an appropriate dose. This result suggests that propofol can be considered as a safe anesthetic agent in surgery during pregnancy at an appropriate concentration. It is likely that the inhibitory effect of PGE_2 synthesis by propofol may contribute to the prevention or reduction of preterm labor or birth after surgery during pregnancy by inhibiting uterine contractions induced by anesthetic agents. However, further studies are necessary to warrant and clinically apply our results.

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