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Original contribution

# Morphologic characteristics of the placental basal plate in in vitro fertilization pregnancies: a possible association with the amount of bleeding in delivery ☆

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**Summary** The aim of the present study was to investigate the relationship between assisted reproductive technology procedures, the morphology of the basal plate of placentas, and amount of bleeding in deliveries. Fifty-five whole placentas (fresh-embryo transfer in the in vitro fertilization cycle [n = 6], frozen-thawed embryo transfer in the natural cycle [n = 13] or in the hormonal cycle [n = 10], and age-matched spontaneously conceived pregnancies [n = 26]) were retrospectively enrolled and histologically analyzed. The whole placentas were stored in our pathological division among 512 singleton pregnancies with vaginal deliveries (34-41 weeks of gestation) at Hamamatsu University Hospital. The morphology of the placental basal plate was examined using Azan staining. A total of 20 digital images (each 0.53 $mm^2$) of microscopic fields were analyzed per placenta to measure the mean values of the vertical maximum thickness of Rohr and Nitabuch fibrinoid layers and % loss of decidua. The thickness of Rohr fibrinoid layer and % loss of decidua were significantly higher in the frozen-thawed embryo transfer in the hormonal cycle group than in the frozen-thawed embryo transfer in the natural cycle and spontaneously conceived pregnancy groups (each $P < .01$). The $z$ scores for both the thickness of Rohr fibrinoid layer and % loss of decidua positively correlated with those for the amount of bleeding in deliveries ($P < .05$ each). Assisted reproductive technology procedures changed the morphology of the placental basal plate, suggesting a possible association with an increase in the amount of bleeding in deliveries.


## 1. Introduction

Assisted reproductive technology (ART) has been widely used for more than a decade to treat infertility. It currently remains unclear whether ART procedures and/or infertility-

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associated factors contribute to adverse outcomes [1–11]. The adverse effects associated with ART in singleton pregnancies have mainly been examined in relation to preterm deliveries, fetal growth restriction, and perinatal mortality [2,3], but few have investigated the relationship between the amount of bleeding in deliveries and ART procedures. Schieve et al [12] reported that ART pregnancies were associated with uterine bleeding; however, the diagnostic criteria of "uterine bleeding" were not described. Hayashi et al [13] reported a significant increase in postpartum hemorrhage in ART pregnancies. Although these limited findings suggested a possible association between ART procedures and the amount of bleeding in deliveries, a consensus has not yet been established.

The blastocyst differentiates into the inner cellular mass or trophectoderm (TE), and the inner cellular mass and trophectoderm eventually form the fetal and placental compartments, respectively [14]. Therefore, it is plausible that not only the fetus but also the placenta may be predisposed to the effects of ART procedures during the early stage of gestation. However, only a few differences have been reported in the placental morphologies of ART pregnancies, such as marginal and velamentous cord insertion and an abnormal placental shape (assessed by the closest placental margin) [15–20].

A hematoma commonly forms between the separating placenta and placental bed as placental separation proceeds, and this hematoma markedly contributes to the amount of total bleeding in delivery; however, this is negligible in some cases [21]. Therefore, morphologic changes in the basal plate of the placenta of ART pregnancies, if present, may be associated with the amount of bleeding. We herein focused on the potential effects of ART procedures on the morphology of the placental basal plate in association with the amount of bleeding in deliveries.

We hypothesized that ART procedures may change the morphology of the basal plates of placentas and be causatively associated with an increase in the amount of bleeding in deliveries. To examine these hypotheses, we retrospectively investigated morphologic changes in the basal plates of placentas (ie, the thickness of Rohr and Nitabuch fibrinoid layers [22-25] and % loss of decidua) as well as the amount of bleeding in deliveries, and then assessed their relationships with ART procedures in pregnancies achieved by fresh-embryo transfer in the in vitro fertilization (IVF) cycle, frozen-thawed embryo transfer in the natural cycle, and frozen-thawed embryo transfer in the hormonal cycle as well as age-matched spontaneously conceived pregnancies.

## 2. Materials and methods

### 2.1. Subjects

Fifty-five whole placentas (fresh-embryo transfer in the IVF cycle [n = 6], frozen-thawed embryo transfer in the natural cycle [n = 13] or in the hormonal cycle [n = 10], and age-matched spontaneously conceived pregnancies [n = 26]) were retrospectively enrolled and histologically analyzed. Three placentas (frozen-thawed embryo transfer in the hormonal cycle) were not enrolled because they were complicated with placenta acreta. The clinical backgrounds of these placentas were obtained from clinical records and summarized in the Table. These whole placentas were stored in our pathological division among 512 singleton pregnancies with vaginal deliveries at Hamamatsu University Hospital between February 2010 and February 2013 (34-41 weeks of gestation). The clinical backgrounds of these 512 singleton pregnancies were obtained from clinical records and summarized in Supplementary Table 2. Subjects were not enrolled if clinical records showed maternal complications including congenital uterine malformations, myoma uteri, adenomyosis, a history of myomectomy when the uterine incision had reached the endometrium, preeclampsia, gestational hypertension, gestational diabetes mellitus, and thrombocytopenia. Cases of vaginal birth after cesarean section were not enrolled.

The amount of bleeding in vaginal deliveries was counted between delivery of the neonate and 2 hours subsequent to delivery of the placenta.

### 2.2. ART procedures

IVF–embryo transfer was performed at 3 institutions: Hamamatsu University Hospital (Hamamatsu Japan), ACT Tower Clinic (Hamamatsu, Japan), and Nishimura Women's Clinic (Hamamatsu, Japan). Fresh embryos were transferred during the IVF cycle, whereas frozen-thawed embryos were transferred during either the natural or hormonal cycle. The oral administration of chlormadinone acetate (6 and 12 mg/d, before and after embryo transfer, respectively) and the

**Table** Embryo transfer cycle, backgrounds, and amount of bleeding in vaginal deliveries, from which the placentas were histologically analyzed

| Embryo transfer cycle | Embryo | n | Maternal age (y) | Weeks of gestation | Birth weight (g) | Bleeding in vaginal deliveries (mL) |
|---|---|---|---|---|---|---|
| IVF cycle | Fresh | 6 | 34.8 ± 3.3 (29-39) | 38.8 ± 0.8 (38-40) | 2817.7 ± 562.9 (2284-3650) | 597.2 ± 592.1 (100-1460) |
| Natural cycle | Frozen thawed | 13 | 34.5 ± 3.3 (28-39) | 39.4 ± 1.4 (37-41) | 3003.5 ± 162.9 (2578-3208) | 425.2 ± 314.8 (22-998) |
| Hormonal cycle | Frozen thawed | 10 | 34.3 ± 3.0 (31-39) | 38.3 ± 2.0 (34-41) | 2826.2 ± 526.7 (2006-3490) | 1098.2 ± 700.4 * (175-2430) |
| Spontaneously conceived pregnancy | | 26 | 34.2 ± 4.2 (28-45) | 39.0 ± 1.4 (35-41) | 2941.5 ± 435.2 (1974-3796) | 859.7 ± 868.2 (70-4050) |

NOTE. Values are the mean ± SD.

* $P < .05$ *vs* the spontaneously conceived pregnancy group.