Antenatal diagnosis of placenta accreta spectrum after in vitro fertilization-embryo transfer: a systematic review and meta-analysis

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Increasing evidence suggests a relationship between in vitro fertilization-embryo transfer (IVF-ET) and placenta accreta spectrum (PAS). Some studies have reported a lower rate of antenatal diagnosis of PAS after IVF-ET compared to PAS with spontaneous conception. This study aimed to review the diagnostic accuracy of PAS after IVF-ET and to explore the relationship between IVF-ET pregnancy and PAS. According to the PRISMA guidelines, a comprehensive systematic review of the literature was conducted through August 31, 2020 to determine the effects of IVF-ET on PAS. In addition, a meta-analysis was conducted to explore the relationship between IVF-ET pregnancy and PAS. Twelve original studies (2011–2020) met the inclusion criteria. Among these, 190,139 IVF-ET pregnancies and 248,534 spontaneous conceptions met the inclusion criteria. In the comparator analysis between PAS after IVF-ET and PAS with spontaneous conception (n = 2), the antenatal diagnosis of PAS after IVF-ET was significantly lower than that of PAS with spontaneous conception (22.2% versus 94.7%, P < 0.01; 12.9% versus 46.9%, P < 0.01). The risk of PAS was significantly higher in women who conceived with IVF-ET than in those with spontaneous conception (odds ratio [OR]: 5.03, 95% confidence interval [CI]: 3.34–7.56, P < 0.01). In the sensitivity analysis accounting for the type of IVF-ET, frozen ET was associated with an increased risk of PAS (OR: 4.60, 95%CI: 3.42–6.18, P < 0.01) compared to fresh ET. Notably, frozen ET with hormone replacement cycle was significantly associated with the prevalence of PAS compared to frozen ET with normal ovulatory cycle (OR: 5.76, 95%CI 3.12–10.64, P < 0.01). IVF-ET is associated with PAS, and PAS after IVF-ET was associated with a lower rate of antenatal diagnosis. Therefore, clinicians can pay more attention to the presence of PAS during antenatal evaluation in women with IVF-ET, especially in frozen ET with hormone replacement cycle.

Placenta accreta spectrum (PAS) is associated with an increased maternal morbidity and mortality due to massive hemorrhage during cesarean delivery1,2. The mean blood loss during cesarean delivery for PAS is approximately 3000 mL, and the hysterectomy rate is around 40%3,5. The main risk factor of PAS is placenta previa, with an approximate odds ratio (OR) of 50–1005,6. Several risk factors have been linked to PAS, including a history of cesarean deliveries (OR: 5–9), uterine surgery (OR: 2–3), multiparity (OR: 3), and advanced maternal age (OR: 2.1)7,8. Recently, mounting evidence have suggested that in vitro fertilization-embryo transfer (IVF-ET) is associated with PAS, and the OR of PAS is roughly between 3 and 1410,11.

IVF-ET currently accounts for 1–4% of live births in the United States and Europe, and the rate has been rapidly increasing as experience with the procedure accumulates and success rates improve14. Similarly, the
number of PAS after IVF-ET may be increasing. Therefore, clinicians should pay attention to patients with PAS after IVF-ET; despite this, little is known about the characteristics of PAS after IVF-ET. Moreover, to the best of our knowledge, no systematic reviews focusing on PAS after IVF-ET have been performed. A recent study has shown that the diagnostic accuracy of PAS by magnetic resonance imaging (MRI) is lower in PAS after IVF-ET than in PAS with spontaneous conception. Therefore, there is a possibility that PAS after IVF-ET has different characteristics, compared to PAS with spontaneous conception.

Several studies have reported that preoperative assessment of PAS disorders and multidisciplinary surgical approaches are needed to decrease the surgical morbidity of patients with PAS. Moreover, it has been widely known that the antenatal diagnosis of PAS helps to reduce hemorrhagic morbidity and improves the prognosis; this may be attributed to the comprehensive multidisciplinary care received by patients, which includes a planned cesarean hysterectomy.

This study focused on assessing whether the diagnostic accuracy for PAS after IVF-ET is lower than that for PAS with spontaneous conception. Furthermore, a meta-analysis was conducted to explore the relationship between IVF-ET pregnancy and PAS.

### Materials and methods

#### Approach for a systematic literature review

A systematic review was performed to review the diagnostic accuracy of PAS after IVF-ET comparing with PAS with spontaneous conception. This study also aimed to examine the effect of IVF-ET on the prevalence of PAS.

#### Eligibility criteria, information sources, search strategy

We conducted a systematic search of articles published through August 31, 2020 using PubMed, Scopus, and Cochrane Central Register of Controlled Trials as performed in our previous study. We reviewed articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies were identified by screening the titles, abstracts, and full texts of relevant articles, as previously described. All abstracts were screened by Sh.M. and Y.N.

The following terms were applied in PubMed, Scopus, and the Cochrane database to identify studies which examined the association between IVF-ET and PAS (Supplemental Table S1; MeSH terms were used in PubMed and Cochrane database search): fertilization in vitro [MeSH] OR Assisted Reproductive Techniques [MeSH Terms] OR Embryo Transfer [MeSH Terms] OR Intracytoplasmic Sperm Injection [MeSH Terms] OR "in vitro fertilization" OR "Cryopreserved" OR "Oocyte donation" OR 'fresh cycle' OR 'frozen cycle' were used to identify the studies regarding IVF-ET.

Studies investigating the effect of IVF-ET on PAS were then identified from this list using the following keywords: Placenta accreta [MeSH Terms] OR "Morbidly adherent placenta" OR "Morbidly adherent placenta" OR "Placenta Accreta Spectrum" OR 'placenta increta' OR "placenta percreta" OR "adherence of placenta" OR "adherence of the placenta" OR "adherent placenta."

#### Study selection

The inclusion criteria based on Patient/Population, Intervention, Comparator, Outcome, Study (PICOS) design are shown in Table 1. Studies were included if they met the following criteria: (1) the effect of IVF-ET on the risk of PAS or antenatal diagnostic accuracy for PAS or maternal outcome for PAS during cesarean delivery was examined; and (2) comparative study was performed between an experimental group and a control group (e.g., IVF-ET versus spontaneous conception, frozen ET versus fresh ET, etc.).

The exclusion criteria were as follows: (1) insufficient information about the outcome of interest; (2) studies lacking control arm; (3) article not written in the English language; and (4) conference abstracts, case reports, case series, reviews, systematic review, and meta-analysis.

#### Data extraction

Data were extracted by the author (Sh.M. and Y.N.) and the following variables were recorded: PAS type, year of study, first author’s name, study location, number of included cases, the definition of PAS, and outcomes of interest (the risk of PAS, maternal outcome, diagnostic accuracy for PAS).

### Table 1. PICOS criteria for inclusion of systematic review. PICOS patient/population, intervention, comparator, outcome, study, PAS placenta accreta spectrum, IVF-ET in vitro fertilization-embryo transfer, ET embryo transfer, FET frozen ET.

| Patient/Population | Intervention | Comparator | Outcome | Study design |
|--------------------|--------------|------------|---------|--------------|
| Pregnant women conceived with spontaneous conception and IVF-ET | IVF-ET | IVF-ET versus spontaneous conception | Diagnostic accuracy of PAS after IVF-ET compared to PAS with spontaneous conception | Retrospective or prospective cohort studies, case-control study, and randomized controlled trials |
Outcome measures analysis and assessment of risk of bias. The primary objective of the study was to review the diagnostic accuracy of PAS after IVF-ET. Two secondary objectives were also examined. First, the relationship between IVF-ET pregnancy and PAS was examined, comparing women who conceived with IVF-ET versus those with spontaneous conception. In the sensitivity analysis, the risk of PAS was examined according to the approach of IVF-ET (fresh ET versus spontaneous conception, frozen ET versus spontaneous conception, fresh ET versus frozen ET, frozen ET with hormone replacement cycle versus frozen ET with normal ovulatory cycle). Second, maternal outcome of PAS after IVF-ET was examined.

Risk of bias assessment was performed using the Risk Of Bias In Non-randomized Studies-of Interventions tool (ROBINS-I)29–31.

Meta-analysis plan. From the eligible study data, the risk of PAS estimates for the experimental and control groups was computed by using the 95% confidence intervals (CIs) of the reported values to estimate the odds ratios for the risk of PAS. Since most studies reported the odds ratio for PAS, the study which showed the risk ratio without showing crude data was excluded from the analysis. Heterogeneity across the studies was examined using I² statistics, which measures the percentage of total variation across studies. The meta-analysis and the production of all graphics were performed using RevMan ver. 5.4.1 software (Cochrane Collaboration, Copenhagen, Denmark). For consistency, data from all outcomes (continuous and bivariate) were entered into RevMan ver. 5.4.1 in such a way that negative effect sizes or relative risks of < 1 favored active intervention.

Statistical analysis. Differences in baseline demographics between the two groups were assessed with Fisher exact test, or chi-square as appropriate. All statistical analyses were based on two-sided hypotheses, and a P-value of less than 0.05 was considered statistically significant. Statistical Package for Social Sciences (IBM SPSS, version 27.0, Armonk, NY) was used for the analysis.

Ethical committee exemption. The approval of Institutional Review Board exempted the use of publicly available data.

Results
Study selection. The study selection schema has been displayed in Fig. 1. A total of 214 studies were examined, and 12 studies, comprising of 190,139 IVF-ET pregnancies and 248,534 pregnancies with spontaneous conception met the inclusion criteria and were used for the descriptive analysis10–12,15,32–39.

Study characteristics. The meta-data of the evaluated studies are shown in Supplemental Table S2. One study was excluded due to the presence of overlapping cases13. The aims of the 12 studies (some studies were overlapping) were as follows: two studies examined the rate of antenatal diagnosis of PAS comparing between PAS after IVF-ET group and PAS with spontaneous conception group11,12,32,34,36–39, eight studies compared the effect of IVF-ET on PAS between IVF-ET group and spontaneous conception group10,12,15,32,34,36–39, three studies compared the prevalence of PAS between frozen ET and fresh ET group11,32,36, and one study compared the prevalence of PAS between frozen ET with hormone replacement cycle and frozen ET with normal ovulatory cycle15. The data on intracytoplasmic sperm injection were unavailable in most studies (n = 10).

No studies focused on the maternal outcomes of PAS after IVF-ET. Moreover, the severity (placenta accreta, increta, and percreta) of PAS was not compared between PAS after IVF-ET and PAS with spontaneous conception.

In the 12 included studies, the patients’ background was matched for maternal age in one study11, and matched for maternal age and parity in the other32. Studies included in this review were published from 2011 to 2020. The majority of the studies were from Japan (58.3%)10,15,32,33,35–37, followed by United States (25.0%)11,38,39, China (8.3%)14, and Israel (8.3%)12.

Risk of bias of included studies. All studies were retrospective and of non-randomized comparative design10–12,15,32–39. No prospective studies were identified. The results of the risk of bias assessment for the comparative studies10–12,15,32–39 showed that there could be a moderate publication bias (moderate quality) in nine studies10–12,15,32–35,37 and severe publication bias (low quality) in three studies (Supplemental Table S3)15,36,37.

Definition of PAS. Among 12 studies, the definition of PAS was mentioned in six11,12,15,36,38,39. Of those, three studies defined PAS as a histopathological proven PAS15,38,39 and the remaining three defined PAS which was diagnosed by histopathological analysis or clinical diagnosis11,12,36.

Meta-analysis. Diagnostic accuracy on PAS after IVF-ET. Two studies compared the antenatal diagnostic accuracy of PAS after IVF-ET (Table 2)15,38, one study determined the diagnostic accuracy of PAS after IVF-ET with placenta previa in MRI (28 cases of PAS)15, and another one investigated the rate of antenatal diagnosis of PAS without placenta previa in ultrasonography (112 cases of PAS)15. The rate of antenatal diagnosis of MRI for placenta previa patients with PAS after IVF-ET was significantly lower 2/9 (22.2%) than that for PAS with spontaneous conception 18/19 (94.7%, P < 0.01)15. Similar to the MRI study, the rate of antenatal diagnosis of ultrasonography for PAS after IVF-ET was significantly lower than that for PAS with spontaneous conception (< 4/31 [< 12.9%] versus 38/81 [46.9%], P < 0.01)15.

These limited data suggested that the rate of antenatal diagnosis for PAS after IVF-ET may be lower than that of PAS with spontaneous conception both in women with and without placenta previa.
The risk of PAS between IVF-ET versus spontaneous conception. Nine studies (two of low and seven of moderate quality) examined the effect of IVF-ET on PAS (Table 3). In nine studies, there were 13,897 patients having IVF-ET pregnancies and 248,474 patients having pregnancies with spontaneous conception. Due to substantial heterogeneity, a random-effect analysis was performed. In the unadjusted pooled analysis \((n=9)\), IVF-ET was associated with an increased risk of PAS (OR: 5.03, 95%CI: 3.34–7.56, \(P<0.01\); heterogeneity: \(P<0.01, I^2=89\%\)) (Fig. 2A). Egger’s test detected the presence of publication bias (\(P<0.01\)). Of these nine studies, the effect of IVF-ET on placenta previa was examined in six. With regard to placenta previa, IVF-ET was associated with an increased risk of placenta previa (OR: 2.79, 95%CI: 2.11–3.69, \(P<0.01\); heterogeneity: \(P<0.01, I^2=71\%\)) (Fig. 2B).

In the patient background-matched comparator analysis of the prevalence of PAS between IVF-ET versus spontaneous conception, a fixed-effect model was used as no heterogeneity was observed between the studies.
cases underwent FET during the ovulation cycle. Controls matched for maternal age, parity, BMI, smoking, alcohol consumption, and pre-existing maternal diseases. Pathological diagnosis, –, not applicable; definition of placenta accreta spectrum, matching patient background matching, previa placenta previa, OR odds ratio, PAS placenta accreta spectrum, IVF in vitro fertilization-embryo transfer, fresh fresh embryo transfer, frozen frozen embryo transfer, FET Frozen embryo transfer, ICSI Intracytoplasmic sperm injection.

In the adjusted pooled analysis (n = 2), IVF-ET was associated with an increased risk of PAS (OR: 2.41, 95% CI: 1.97–2.94, P < 0.01; heterogeneity: P = 0.74, I² = 0%) (Fig. 2C). The risk of publication bias could not be calculated due to the small number of studies.

The risk of PAS: spontaneous conception versus fresh ET versus frozen ET. To determine the risk of IVF-ET on PAS according to the type of IVF-ET (spontaneous conception versus fresh ET, spontaneous conception versus frozen ET, fresh ET versus frozen ET), a sensitivity analysis was performed. Two studies were identified to examine the risk of fresh ET versus frozen ET on PAS compared to that on spontaneous conception patients. Among the two studies, there were 1378 fresh ET patients, 280 frozen ET patients, and 54,024 spontaneous conception patients. A fixed-effect analysis was performed due to the absence of heterogeneity. In the comparator analysis between fresh ET versus spontaneous conception (n = 2), PAS patients were more likely to be observed in the fresh ET group compared to that of the spontaneous conception group (OR: 3.04, 95% CI: 2.15–4.28, P < 0.01; heterogeneity: P = 0.85, I² = 0%) compared to that of fresh ET (Fig. 3C). The risk of publication bias could not be calculated due to the small number of studies.

To determine whether fresh ET or frozen ET is a stronger risk factor of PAS, three studies were included in the analysis (one of low and two of moderate quality)1,3,36. Of those, there were 91,063 frozen ET patients and 51,833 fresh ET patients, respectively. Since no heterogeneity was observed, a fixed effect analysis was performed. In the pooled analysis (n = 3), frozen ET was associated with an increased risk of PAS (OR: 4.60, 95% CI: 3.42–6.18, P < 0.01; heterogeneity: P = 0.42, I² = 0%) compared to that of fresh ET (Fig. 3C). The risk of publication bias could not be calculated due to the small number of studies. One study compared the rate of placenta previa between frozen ET versus fresh ET35. In this study, frozen ET was associated with a decreased rate of placenta previa compared to fresh ET (OR: 0.80, 95% CI: 0.70–0.89, P < 0.01).

The risk of PAS: frozen ET with hormone replacement cycle versus frozen ET with normal ovulatory cycle. One comparator study examined the prevalence of PAS between frozen ET with hormone replacement cycle versus frozen ET with normal ovulatory cycle groups (Table 4)35. This study did not include spontaneous conception patients and included only women with frozen ET. In this comparator analysis, frozen ET with hormone replacement cycle was significantly associated with the prevalence of PAS compared to that of frozen ET with normal ovulatory cycle (OR: 5.76, 95% CI: 3.12–10.64, P < 0.01). The rate of placenta previa was similar between the two groups (OR: 0.80, 95% CI: 0.59–1.08, P = 0.15).

| Author          | Salmanian38 | Modest39 | Tanaka37 | Sakai36 | Nagata36 | Zhu34 | Kasar11 | Hayashi32 | Esh-Broder32 |
|-----------------|-------------|----------|----------|---------|----------|-------|---------|----------|-------------|
| Year            | 2020        | 2020     | 2019     | 2019    | 2016     | 2015  | 2012    | 2011     |             |
| n               | 37,461      | 28,344   | 6952     | 735     | 91,982   | 7923  | 54,947  | 8834     | n = 25,193  |
| Control         | 36,890      | 26,926   | 6141     | 648     | 90,506   | 5282  | 53,376  | 4264     | 24,441      |
| IVF             | 571         | 1418     | 811      | 87      | 1476     | 2641  | 1571    | 4570     | 752         |
| Fresh           | –            | –        | 81       | 275     | –        | –     | 1351    | –        | –           |
| Frozen          | –            | –        | 730      | 60      | –        | –     | 220     | –        | –           |
| ICSI            | –            | –        | –        | –       | 34/87 (39.1) | – | 314/2641 (11.9) | – | –           |

Table 3. Comparator analysis of PAS between women with IVF-ET and those with non-IVF-ET. The numbers (percentages per column) are shown. *Included cases without cesarean hysterectomy. **Two cases underwent FET during the ovulation cycle. ° Controls matched for maternal age, parity, BMI, smoking, alcohol consumption, and pre-existing maternal diseases. Path histopathological diagnosis, clin clinical diagnosis, –, not applicable; definition of placenta accreta spectrum, matching patient background matching, previa placenta previa, OR odds ratio, PAS placenta accreta spectrum, IVF in vitro fertilization-embryo transfer, fresh fresh embryo transfer, frozen frozen embryo transfer, FET Frozen embryo transfer, ICSI Intracytoplasmic sperm injection.
A  PAS: IVF-ET versus spontaneous conception (not matched)

| Study       | log [Odds Ratio] | SE   | Weight | Odds Ratio            | Year |
|-------------|------------------|------|--------|-----------------------|------|
| Esh-Broder  | 2.58             | 0.3436 | 9.8%   | 13.20 [6.73, 25.88]   | 2011 |
| Hayashi     | 0.7866           | 0.1366 | 12.6%  | 2.20 [1.68, 2.87]     | 2012 |
| Kaser       | 1.3764           | 0.1486 | 12.4%  | 3.96 [2.96, 5.30]     | 2015 |
| Zhu         | 0.868            | 0.1074 | 12.8%  | 2.38 [1.93, 2.94]     | 2016 |
| Sakai       | 2.3547           | 0.3419 | 9.8%   | 10.53 [5.39, 20.59]   | 2019 |
| Nagata      | 1.8118           | 0.2555 | 11.1%  | 6.12 [3.71, 10.10]    | 2019 |
| Salmanian   | 1.0972           | 0.3264 | 10.0%  | 3.00 [1.58, 5.68]     | 2020 |
| Tanaka      | 2.0438           | 0.3355 | 9.9%   | 7.72 [4.00, 14.90]    | 2020 |
| Modest      | 2.0543           | 0.2129 | 11.7%  | 7.80 [5.14, 11.84]    | 2020 |

Total (95% CI) 100.0% 5.03 [3.34, 7.56]

Heterogeneity: Tau² = 0.33; Chi² = 75.23, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 7.76 (P < 0.00001)

B  Placenta previa: IVF-ET versus spontaneous conception (not matched)

| Study     | log [Odds Ratio] | SE   | Weight | Odds Ratio          | Year |
|-----------|------------------|------|--------|---------------------|------|
| Hayashi   | 0.7866           | 0.1366 | 21.2%  | 2.20 [1.68, 2.87]   | 2012 |
| Kaser     | 1.448            | 0.4007 | 8.6%   | 4.25 [1.94, 9.33]   | 2015 |
| Zhu       | 0.7642           | 0.1073 | 23.0%  | 2.15 [1.74, 2.65]   | 2016 |
| Nagata    | 1.5268           | 0.1745 | 18.9%  | 4.60 [3.27, 6.48]   | 2019 |
| Salmanian | 0.8771           | 0.3255 | 11.1%  | 2.40 [1.27, 4.55]   | 2020 |
| Tanaka    | 1.0131           | 0.203  | 17.2%  | 2.75 [1.85, 4.10]   | 2020 |

Total (95% CI) 100.0% 2.79 [2.11, 3.69]

Heterogeneity: Tau² = 0.08; Chi² = 17.03, df = 5 (P = 0.004); I² = 71%
Test for overall effect: Z = 7.20 (P < 0.00001)

C  PAS: IVF-ET versus spontaneous conception (matched)

| Study   | log [Odds Ratio] | SE   | Weight | Odds Ratio            | Year |
|---------|------------------|------|--------|-----------------------|------|
| Hayashi | 0.983            | 0.3226 | 10.0%  | 2.67 [1.42, 5.03]     | 2012 |
| Zhu     | 0.868            | 0.1074 | 90.0%  | 2.38 [1.93, 2.94]     | 2016 |

Total (95% CI) 100.0% 2.41 [1.97, 2.94]

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 8.83 (P < 0.00001)

Figure 2. Results of the meta-analysis for the effect of IVF-ET on PAS. The pooled odds ratio for (A) PAS, (B) placenta previa, and (C) PAS (patient background matched) between IVF-ET patients versus spontaneous conception patients are shown. Since the numbers after the third decimal places for the lower or upper confidence interval were omitted in most studies, some calculated values of OR using Revman ver. 5.4.1™ may be different from the original values. Abbreviations: PAS, placenta accreta spectrum; OR, odds ratio; CI, confidence interval; and IVF-ET, in vitro fertilization-embryo transfer.

Discussion

Main findings. The key findings of this study are the following: (i) the rate of antenatal diagnosis of PAS after IVF-ET may be lower than that of PAS with spontaneous conception, and (ii) IVF-ET was associated with an increased risk of PAS, especially in women who conceived with frozen ET with hormone replacement cycle.
Comparison with existing literature. Several studies have reported that IVF-ET is associated with an increased risk of PAS. The first study that showed the relationship between IVF-ET and PAS was published in 2011, but it did not determine the risk of PAS according to the type of IVF-ET. Subsequently, Kaser et al. examined the risk of PAS in different groups (spontaneous conception \( n = 53,376 \), fresh ET \( n = 1,351 \), and frozen ET \( n = 220 \)). The authors found that women with an endometrial thickness of < 9 mm before ET had a greater risk of PAS than women with an endometrial thickness of ≥ 9 mm; thus, a thin endometrium may lead to PAS. In their analysis, the median endometrial thickness before ET was 8.4 mm in the frozen ET cycle and...
A systematic review and meta-analysis that compared the risk of obstetrics complication showed no significant differences in the risk of placenta previa between the frozen ET and fresh ET groups (adjusted OR 0.70, 95% CI 0.46–1.08), which was consistent with our results.63 These data support our findings suggesting that PAS can occur after IVF independently of the placentation position.

We should note some limitations of this study in examining the effects of IVF-ET on the risk of PAS between women who conceived with IVF-ET and spontaneous conception. Advanced maternal age, increased parity, and prior cesarean delivery are the main risk factors for the development of placenta previa, and PAS in subsequent pregnancies has been reported in numerous large studies.14 In general, women who require IVF to conceive are more often older and more likely to have a history of uterine surgery, including cesarean delivery or dilatation and curettage, compared with women who conceived with spontaneous conception.99–102 We should note that these factors are the risk factors of placenta previa and PAS.

### Table 4. Comparator analysis of PAS between frozen ET versus fresh ET groups.

| Author       | Year | Area | Control | IVF | Fresh | Frozen | Definition | PAS |
|--------------|------|------|---------|-----|-------|--------|------------|-----|
| Sakai11      | 2019 | JPN  | 648     | 87  | 27    | 60     | Path, clin | 19.2 |
| Takeshima33  | 2016 | JPN  | –       | 141,238 | 50,455 | 90,783 | Path, clin | –   |
| Kaser11      | 2015 | USA  | –       | 1571 | 1351  | 220    | Path, clin | –   |
| Saito35      | 2019 | JPN  | –       | –   | –     | –      | 11/10,755 | –   |

10.6 mm in the fresh ET cycle. Therefore, frozen ET is considered a higher risk factor for PAS compared to that of fresh ET. Our systematic review found that Kaser et al.’s study is the only study that determined the association between endometrial thickness and PAS. From the results of the meta-analysis, frozen ET with hormone replacement cycle appeared to be the most significant risk factor of PAS (Fig. 3A–D). Saito et al. compared the prevalence of PAS between women who conceived with frozen ET with hormone replacement cycle and those who conceived with frozen ET with normal ovulatory cycle.35 They found that frozen ET with hormone replacement cycle is more likely to be complicated with PAS than frozen ET with normal ovulatory cycle. Although Saito et al.’s study did not examine the endometrial thickness, several studies have reported that endometrial thickness is lower in women who conceived with frozen ET with hormone replacement cycle than in those who conceived with frozen ET with normal ovulatory cycle or fresh ET.36–42 Thus, our results are consistent with those of Kaser et al.’s study.

To discuss the relationship between IVF-ET and PAS, it is pertinent to mention that IVF-ET is associated with an increased rate of placenta previa, and placenta previa, in turn, is a high-risk factor for PAS (OR: 50–100).6–8 Therefore, it is possible that an increased risk of placenta previa contributes to an increased prevalence of PAS. A previous study that examined the relationship between endometrial thickness and placenta previa revealed that the risk of placenta previa is increased in women with an endometrial thickness of >12 mm (adjusted OR: 3.74, 95%CI: 1.90–7.34) compared with women with an endometrial thickness of <9 mm.42 In contrast, Kaser et al.’s study did not examine the endometrial thickness of <9 mm before ET had a greater risk of PAS.11

In our analysis, frozen ET was found to be associated with an increased risk of PAS compared to fresh ET, whereas the rate of placenta previa was not found to increase in the frozen ET group. Similarly, frozen ET with hormone replacement cycle is associated with an increased rate of PAS compared to frozen ET with normal ovulatory cycle, whereas the rate of placenta previa was similar between the two groups (Table 4). This study includes a comparator analysis to examine the association between IVF-ET and PAS. Since we did not focus on IVF-ET and placenta previa, our analysis missed a large study that compared the rate of placenta previa between women who conceived with fresh ET and frozen ET.43

A systematic review and meta-analysis that compared the risk of obstetrics complication showed no significant differences in the risk of placenta previa between the frozen ET and fresh ET groups (adjusted OR 0.70, 95%CI 0.46–1.08), which was consistent with our results.63 These data support our findings suggesting that PAS can occur after IVF independently of the placentation position.
Since previous studies did not match the obstetric patient background or most studies did not perform a multivariate analysis with adjustments of various background factors in obstetrics patients, such as those mentioned above, our analysis cannot attribute IVF-ET as the risk factor of PAS while excluding the confounding factors.

We also should note that the quality of the diagnosis of PAS in this study may be low due to the following reasons: (i) all studies did not mention the severity or classification of PAS according to the previous literature, and (ii) all studies did not report the detailed clinical findings at delivery and/or the histopathologic data. Therefore, there is a possibility that the present study has included women with less severe PAS (i.e., placenta adherent or creta) rather than women with the more severe type of PAS (i.e., placenta increta or percreta). This is a strong limitation of this study, and further studies examining the effect of IVF-ET on the severity of PAS are warranted.

In summary, a lower endometrial thickness before ET may be associated with an increased risk of PAS; thus, confirmation of the endometrial thickness in women who have additional high-risk factors for PAS is recommended. Further studies investigating the relationship between endometrial thickness before ET and PAS are warranted.

The main cause of PAS, except for placenta previa, is damage to the endometrium-myometrial interface due to prior uterine surgeries, especially cesarean delivery. These surgeries lead to abnormal decidualization in the area of the uterine scar, as well as myometrial invasion of the trophoblast and villi. Previous studies have reported that an abnormally rich vascularity between the cesarean scar and placenta is observed in cases of PAS with uterine scars, even in early pregnancy. Unlike the typical cause of PAS with spontaneous conception, a thin endometrial thickness may be associated with PAS after IVF-ET. It is speculated that abnormal vessels between the uterine scar and placenta are not newly developed in cases of PAS after IVF-ET without uterine scar; thus, the representative ultrasound or MRI findings are not observed due to the differences in the mechanisms of PAS. No studies have yet identified the specific findings of ultrasound or MRI in PAS after IVF-ET.

Although IVF-ET is associated with an increased risk of PAS, no study has yet compared the effects of IVF-ET on PAS with spontaneous conception. PAS complicated with placenta previa is one of the highest risk factors of massive postpartum hemorrhage. Moreover, PAS after IVF-ET is associated with a lower rate of antenatal diagnosis. Therefore, if IVF-ET is associated with an increased risk of PAS in women with placenta previa, clinicians can be more aware of the presence of PAS in patients with placenta previa who have conceived with IVF-ET. On the other hand, since the technical ability for the antenatal diagnosis of PAS has been clearly shown in the literature, we must appreciate the technical limitations of our diagnostic capabilities for PAS after IVF-ET.

Given the results of this study, it is important to anticipate that women who undergo IVF, especially frozen ET with hormone replacement cycle, are at increased risk for PAS which is difficult to identify antenatally, and some points as follows may be beneficial for the patients: (i) appropriate counseling prior to ET may be beneficial, as some women who have had successful pregnancies may not wish to assume this risk if known ahead of time, (ii) thorough and careful evaluations of the placenta by experienced sonologists and radiologists are key to identifying cases of PAS after IVF-ET, and (iii) preparations for the unidentified PAS after IVF-ET may help reduce hemorrhagic morbidity and improve prognosis, possibly because of multidisciplinary care, which includes cesarean hysterectomy, uterine artery embolization, transfusion preparation, and treatment by skilled physicians.

**Strengths and limitations.** The strengths of the study are that this is the first systematic review to focus on PAS after IVF-ET. Our study revealed that IVF-ET is associated with the prevalence of PAS, and this risk appeared to be highest in women who conceived with frozen ET with hormone replacement cycle. However, this study has some limitations. First, there was an unmeasured bias due to the retrospective studies we included in our systematic review. Potential sources of confounding variables in the study include the following: the varying definition of PAS across studies, the unmatched patient background, the lack of specific reasons for infertility, and the severity of PAS was not examined.

Second, the quality of the diagnosis of PAS appears to be low in most studies. Notably, all studies did not mention the severity of PAS and did not report the detailed clinical findings at delivery and/or the histopathologic data of PAS. Therefore, many of the studies included in the present study may have simple PAS rather than the severe one. This is a notable limitation of this study; hence, it should be considered while interpreting the results and the study’s discussion for the patients having IVF-ET. Third, none of the studies matched the obstetric patient background to examine the effects of IVF-ET on the prevalence of PAS; thus, this study cannot isolate IVF-ET as the risk factor of PAS while excluding the confounding factors. This is an important limitation of this study.

Fourth, publication bias is a concern because the negative relationship between IVF-ET and PAS might not have been reported in the original papers. Egger’s test detected severe publication bias in the comparator analysis of the risk of PAS between IVF-ET versus spontaneous conception. This is another important limitation of this study. Fifth, only two studies examined the diagnostic accuracy of PAS after IVF-ET. To clearly show the accuracy of our findings, a more robust study should be conducted. Since a randomized controlled study is difficult due to the rarity of PAS after IVF-ET, a prospective study seems appropriate.

Lastly, the sample size was limited, particularly for the examination of the antenatal diagnosis for PAS after IVF-ET. Moreover, no prospective studies compared the prevalence of PAS among different groups (spontaneous conception versus fresh ET versus frozen ET with normal ovulatory cycle versus frozen ET with hormone replacement cycle).

**Conclusions.** The antenatal diagnosis of PAS after IVF-ET was found to be significantly lower than that of PAS with spontaneous conception. Since IVF-ET is associated with an increased risk of PAS, we believe that clinicians can be more vigilant in ruling out “PAS after IVF-ET” in women with placenta previa who conceive with IVF-ET. To confirm the results of this study, further studies examining the diagnostic accuracy of PAS after
IVF-ET are warranted. Future studies should also examine the risk of PAS among different types of IVF-ET to determine which type has the highest risk for PAS.

Data availability
All the studies used in this study are published in the literature.

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