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Full length article

Risk factors for placenta accreta spectrum in pregnancies conceived after frozen–thawed embryo transfer in a hormone replacement cycle

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ABSTRACT

Objective: Assisted reproductive technology (ART), especially frozen–thawed embryo transfer (FET) in a hormone replacement cycle (HRC), is a risk factor for placenta accreta spectrum (PAS). This study aimed to clarify the risk factors for PAS related to the maternal background and ART techniques in pregnancies achieved after FET in an HRC.

Study design: We performed a case–control study in two tertiary perinatal centres in Japan. Among 14,028 patients who delivered at ≥24 weeks of gestation or were transferred after delivery to two tertiary perinatal centres between 2010 and 2021, 972 conceived with ART and 13,056 conceived without ART. PAS was diagnosed on the basis of the FIGO classification for the clinical diagnosis of PAS or retained products of conception after delivery at ≥24 weeks of gestation. We excluded women with fresh embryo transfer, FET with a spontaneous ovulatory cycle, a donor oocyte cycle, and missing details of the ART treatment. Finally, among women who conceived after FET in an HRC, 62 with PAS and 340 without PAS were included in this study. Multivariate logistic regression models were used for case–control comparisons, with adjustment for maternal age at delivery, parity, endometriosis or adenomyosis, the number of previous uterine surgeries of caesarean section, myomectomy, endometrial polypectomy or endometrial curettage, placenta previa, the stage of transferred embryos, and endometrial thickness at the initiation of progestin administration.

Results: PAS was associated with ≥2 previous uterine surgeries (adjusted odds ratio, 3.57; 95 % confidence interval, 1.60–7.97) and the stage of embryo transfer (blastocysts: adjusted odds ratio, 2.89; 95 % confidence

Abbreviations: ART, assisted reproductive technology; CS, caesarean section; EmT, endometrial thickness; ET, embryo transfer; FET, Frozen–thawed embryo transfer; HRC, hormone replacement cycle; PAS, Placenta accreta spectrum; SOC, spontaneous ovulatory cycle.

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interval, 1.15–7.26). In patients with <2 previous uterine surgeries, PAS was associated with an endometrial thickness of <7.0 mm (adjusted odds ratio, 5.18; 95 % confidence interval, 1.10–24.44).
Conclusion: Multiple uterine surgeries and the transfer of blastocysts are risk factors for PAS in pregnancies conceived after FET in an HRC. In women with <2 previous uterine surgeries, a thin endometrium before FET is also a risk factor for PAS in these pregnancies.

Introduction

Placenta accreta spectrum (PAS) is defined as abnormal adhesion of the placenta to the uterine wall after delivery due to direct placental trophoblast invasion into the myometrium [1]. PAS is a serious and life-threatening complication in pregnancy that involves massive postpartum haemorrhage and often requires caesarean hysterectomy [2–4]. Retained products of conception following delivery at ≥24 weeks of gestation occur mostly as a consequence of focal placenta accreta [5,6]. In developed countries, the prevalence of PAS has increased by approximately 10-fold over the last four decades [1,7].

The risk factors for PAS include placenta previa, a history of uterine surgery, uterine manipulation, advanced maternal age, and adenomyosis [8–10]. Recently, assisted reproductive technology (ART) has been reported to be another risk factor for PAS [11,12].

Frozen–thawed embryo transfer (FET) in a hormone replacement cycle (HRC) is a common ART procedure, but this procedure has the highest risk of PAS [13]. FET has 4.6 times the odds ratio (OR) of PAS compared with fresh embryo transfer (ET) [13]. Additionally, FET in an HRC has approximately 6 times the OR of PAS compared with an HRC in a spontaneous ovulatory cycle (SOC) [13]. However, to the best of our knowledge, no studies have investigated the risk factors for PAS related to the maternal background and ART techniques, exclusively in pregnancies after FET in an HRC. Therefore, this study aimed to clarify the risk factors related to PAS in pregnancies conceived after FET in an HRC by retrospectively analysing maternal clinical parameters, including the details of infertility treatment.

Material and methods

Subjects

This case–control study included Japanese pregnant or puerperal women with and without PAS among those who conceived after FET in an HRC and were admitted to Kurume University Hospital or St. Mary's Hospital. These two tertiary perinatal centres manage almost all high-risk pregnancies (total number of births is approximately 10,000/year). Among the 14,028 women who delivered at ≥24 weeks of gestation or were transferred after delivery to these tertiary perinatal centres between January 2010 and March 2021, 972 (6.9 %, 972/14,028) conceived after ART and 13,056 conceived without ART (Fig. 1). Among the 972 women who conceived after ART, 68 (7.0 %, 68/972) were diagnosed with PAS on the basis of the FIGO classification for the clinical diagnosis of PAS [14]. Among the 68 patients diagnosed with PAS, after excluding 6 patients (1 patient with fresh ET and 5 patients with FET with an SOC), the remaining 62 patients were allocated to the PAS group. The 62 patients with PAS included 49 with a grade 1, abnormal adherent placenta, 2 with grade 2, abnormally invasive placentation, and 11 with retained products of conception after delivery (36–41 weeks). In this study's cohort, only one patient was diagnosed with PAS prenatally, resulting in elective caesarean section (CS) at 36 weeks of gestation. Among the 904 women who were not diagnosed with PAS, we excluded 172 with fresh ET, 170 with FET with an SOC, 11 with a donor oocyte cycle, and 211 with missing details of the ART treatment. The remaining 340 women with FET in an HRC were regarded as controls (non-PAS group). All patients in the PAS group (n = 62) and women in the non-PAS group (n = 340) conceived after an autologous oocyte cycle. There were 58 patients with a singleton pregnancy and 4 patients with a twin pregnancy in the PAS group, and 308 women with a singleton pregnancy and 32 women with a twin pregnancy in the non-PAS group.

Definition of parameters

The parameters of maternal clinical background and ART-related items were retrieved from the medical records of three hospitals and 13 ART clinics (Supplemental Table 1). The history of uterine surgery included CS, myomectomy (laparotomic or laparoscopic), endometrial polypectomy including hysteroscopic surgery, and endometrial curettage for induced abortion or after spontaneous miscarriage. The number of previous uterine surgeries in each woman was counted and categorised into 0, 1, and ≥2.

Statistical methods

Continuous variables were analysed using the Mann–Whitney *U* test. Categorical variables were analysed using the chi-square test, and Fisher's exact test was used when there were five or fewer variables. A logistic regression analysis was performed to extract factors associated with PAS. The adjustment factors were maternal age at delivery, parity,

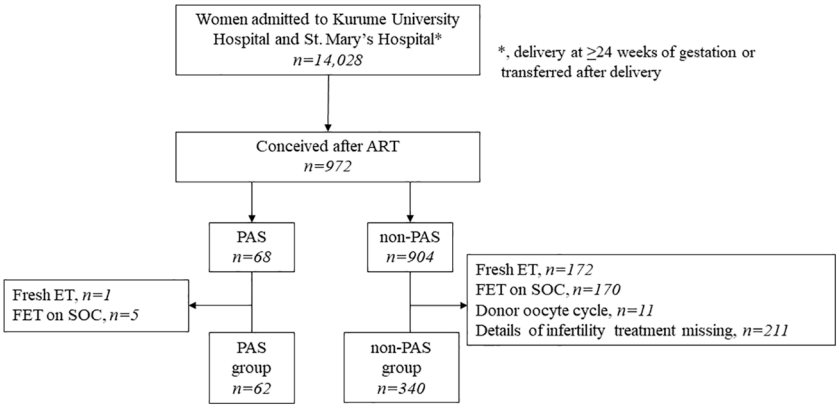

Fig. 1. Flow diagram of the study population. ET, embryo transfer; FET, frozen–thawed embryo transfer; ART, assisted reproductive technology; PAS, placenta accreta spectrum; SOC, spontaneous ovulatory cycle.

endometriosis or adenomyosis, the number of previous uterine surgeries, placenta previa, the stage of the transferred embryo, and endometrial thickness (EmT) at the initiation of progestin administration in the cycle at conception, resulting in pregnancy. Adjustment factors with missing data or a sparse cell frequency count were excluded. A p value <0.05 indicated statistical significance. Analyses were performed using STATA/MP16.0 (StataCorp LLC, College Station, TX, USA).

Ethical statement

This study was approved by the Institutional Review Board of Kurume University, School of Medicine (No. 20145).

Results

Clinical background

Table 1 shows the clinical background of the women with and those without PAS. Among the types of uterine surgeries, the rate of endometrial curettage was significantly higher in the PAS group than in the non-PAS group ($p = 0.046$).

Relationship between PAS and the number of previous uterine surgeries

Table 2 shows the number of uterine surgeries between the groups. The rate of previous uterine surgery was significantly higher in the PAS group than in the non-PAS group ($p = 0.015$).

Table 1
Comparison of the clinical parameters of medical background and obstetric complications between the PAS and non-PAS groups.

Parameters	PAS (n = 62)		non-PAS (n = 340)		*p*-value
Medical background					
Maternal age at embryo transfer (y)	35	(25–43)	36	(25–45)	*0.287*
Maternal age at delivery (y)	36	(26–43)	37	(25–45)	*0.255*
Gravidity	2	(1–6)	2	(1–6)	*0.670*
Parity	0	(0–2)	0	(0–3)	*0.871*
BMI before pregnancy (kg/m^2)	20	(16–30)	21	(15–36)	*0.141*
Smoking habits, n (%)					
Before pregnancy	8	(13)	38	(11)	*0.629*
During pregnancy	2	(3)	8	(2)	*0.668*
Endometriosis or adenomyosis, n (%)	8	(13)	34	(10)	*0.470*
Uterine abnormality, n (%)	0	(0)	1	(0)	*0.669*
History of uterine surgery, n (%)	32	(52)	125	(37)	*0.029*
Caesarean section	8	(13)	33	(10)	*0.444*
Endometrial polypectomy	6	(10)	17	(5)	*0.145*
Endometrial curettage	19	(31)	66	(19)	*0.046*
Myomectomy	7	(11)	29	(9)	*0.485*
History of PAS, n (%)	1	(2)	1	(0)	*0.246*
Hyperthyroidism, n (%)	0	(0)	9	(3)	*0.356*
Hypothyroidism, n (%)	4	(6)	32	(9)	*0.629*
Diabetes mellitus, n (%)	1	(2)	0	(0)	*0.154*
Chronic hypertension, n (%)	0	(0)	6	(2)	*0.596*
Uterine fibroids, n (%)	3	(5)	20	(6)	*1.000*
Asherman syndrome, n (%)	1	(2)	0	(0)	*0.154*
Obstetric complications					
Placenta previa, n (%)	2	(3)	5	(1)	*0.373*
Gestational hypertension, n (%)	1	(2)	7	(2)	*1.000*
Pre-eclampsia, n (%)	6	(10)	38	(11)	*0.728*
Gestational diabetes mellites, n (%)	3	(5)	38	(11)	*0.171*
Premature birth (<37 weeks), n (%)	6	(10)	30	(9)	*0.829*

BMI, body mass index; PAS, placenta accreta spectrum. Data are shown as n (%) or the median (range).

Table 2
Comparison of the number of uterine surgeries between the PAS and non-PAS groups.

	PAS (n = 62) n (%)		non-PAS (n = 340) n (%)		*p*-value
Number of uterine surgeries					*0.015*
0	30	(48)	215	(63)	
1	19	(31)	93	(27)	
≥2	13	(21)	32	(9)	

PAS, placenta accreta spectrum.

Details of ART treatment

Table 3 shows the details of the ART treatment in the groups. The stage of the transferred embryo was significantly different between the groups ($p = 0.013$). In the clinical setting, when blastocysts are being transferred, a single embryo is preferred, whereas in cases of cleavage-stage embryo transfer, there is an increased likelihood of transferring two embryos. Consequently, the embryo stage and the number of embryos are interrelated. Therefore, to avoid collinearity, the number of transferred embryos was excluded in the following multivariate analysis.

Associations between PAS and clinical parameters

Table 4 shows the results of the multivariate analysis of risk factors associated with PAS. PAS was associated with ≥2 previous uterine

Table 3
Comparison of the clinical parameters of infertility treatment between the PAS and non-PAS groups.

Parameters	PAS (n = 62)		non-PAS (n = 340)		*p*-value
Indication					*0.371*
Tubal factor, n (%)	15	(24)	106	(31)	
Male factor, n (%)	14	(23)	56	(17)	
Others, n (%)	33	(53)	178	(52)	
IVF method					*0.986*
Conventional IVF, n (%)	36	(58)	197	(58)	
Intracytoplasmic sperm injection, n (%)	26	(42)	143	(42)	
Age of women during embryo creation	35	(24–43)	36	(25–45)	*0.211*
Duration from freezing to thawing embryos (months)	4	(1–47)	3	(1–76)	*0.592*
Stage of transferred embryos					*0.013*
Cleavage stage, n (%)	6	(10)	70	(21)	
Blastocyst, n (%)	55	(89)	242	(71)	
Cleavage stage and blastocyst, n (%)	1	(2)	28	(8)	
Number of transferred embryos	1	(1–2)	1	(1–3)	*0.002*
Administration route of oestrogen					*0.957*
Transdermal, n (%)	59	(95)	323	(95)	
Oral, n (%)	3	(5)	17	(5)	
Administration route of progesterone					*0.166*
Vaginal, n (%)	46	(74)	279	(82)	
Oral, n (%)	8	(13)	20	(6)	
Intramuscular, n (%)	2	(3)	5	(1)	
Oral and intramuscular, n (%)	6	(10)	36	(11)	
Endometrial thickness (mm)	9.5	(6.2–16.2)	10.0	(4.5–17.0)	*0.179*
Endometrial thickness <7.0 mm, n (%)	3	(5)	7	(2)	*0.189*
Peak serum oestradiol concentration (pg/ml)	244	(93–826)	235	(46–1079)	*0.661*

PAS, placenta accreta spectrum; IVF, *in vitro* fertilisation. Data are shown as n (%) or the median (range).

Table 4
Association between PAS and clinical parameters.

Parameters	Adjusted odds ratio	95 % confidence interval	*p*-value
Maternal age at delivery	0.96	0.90–1.03	*0.255*
Parity	0.80	0.48–1.35	*0.407*
Endometriosis or adenomyosis	1.42	0.60–3.39	*0.431*
Placenta previa	2.78	0.48–16.15	*0.284*
Number of previous uterine surgeries			
0	1.00		
1	1.56	0.81–3.01	*0.182*
≥2	3.57	1.60–7.97	*0.002*
Stage of transferred embryo			
Cleavage stage	1.00		
Blastocyst	2.89	1.15–7.26	*0.024*
Cleavage stage and blastocyst	0.44	0.05–3.97	*0.468*
EmT <7.0 mm	2.00	0.47–8.46	*0.345*

PAS, placenta accreta spectrum; EmT, endometrial thickness.

surgeries (adjusted OR, 3.57; 95 % confidence interval [CI], 1.60–7.97) and the stage of the transferred embryo (blastocysts: adjusted OR, 2.89; 95 % CI, 1.15–7.26). Exploratory multivariate analysis was also performed in a sub-group of women with <2 previous uterine surgeries. Supplemental Tables 2 and 3 show the clinical background and the clinical parameters of infertility treatment in women with and those without PAS with <2 uterine surgeries. Table 5 shows the results of the multivariate analysis of risk factors associated with PAS in women with <2 uterine surgeries. In women with <2 uterine surgeries, PAS was associated with an EmT of <7.0 mm (adjusted OR, 5.18; 95 % CI, 1.10–24.44).

Discussion

A history of uterine surgery, including CS, operative hysteroscopy, and endometrial curettage, is a major risk factor for PAS in the general population [8–10]. The relationship between PAS and a history of CS has been extensively studied [15–18]. Any damage to the endometrium may cause PAS after conception, particularly in women with a history of uterine surgery [19]. One of the pathological characteristics of the placenta in cases with PAS is the formation of thick fibrinoid deposits at the uteroplacental interface [20]. Myometrial damage from uterine surgery, characterised by disarray of myofibers, tissue oedema, inflammation, and elastosis, can lead to abnormal decidualisation [19]. Such damage may cause the invasion of extravillous trophoblasts into radial and/or arcuate arteries, resulting in high-velocity maternal blood entering the intervillous space. To the best of our knowledge, the present study is the first to quantitatively analyse the effect of a history of four types of uterine surgeries, CS, myomectomy, curettage and endometrial polypectomy, on the risk of PAS in women who conceived after ART.

Table 5
Association between PAS and clinical parameters in women with <2 previous uterine surgeries.

Parameters	Adjusted odds ratio	95 % confidence interval	*p*-value
Maternal age at delivery	0.96	0.89–1.05	*0.431*
Parity	0.77	0.41–1.46	*0.431*
Endometriosis or adenomyosis	1.45	0.58–3.63	*0.435*
Placenta previa	2.70	0.47–16.65	*0.266*
Number of previous uterine surgeries			
0	1.00		
1	1.53	0.79–2.98	*0.204*
Stage of transferred embryo			
Cleavage stage	1.00		
Blastocyst	2.59	0.96–7.03	*0.061*
Cleavage stage and blastocyst	0.64	0.07–5.93	*0.696*
EmT <7.0 mm	5.18	1.10–24.44	*0.038*

PAS, placenta accreta spectrum; EmT, endometrial thickness.

In this study, we found that ≥2 previous uterine surgeries were an independent risk factor for PAS. Moreover, this study suggests that intrauterine manipulations, particularly curettage for spontaneous abortion, would be minimised in those who are current or future candidates of ART, including FET. In addition, pregnancy achieved through FET in an HRC, particularly in women with risk factors, should be considered at risk for the development of PAS. The primary cause of PAS is a history of uterine surgery [1]. However, some reports have shown that PAS associated with *in vitro* fertilisation has a cause other than a history of uterine surgery [21], and a thin endometrium might be another risk factor for PAS [22]. Therefore, we also examined the association of PAS with <2 previous uterine surgeries. On the basis of previous studies, we set the cut-off value of 7 mm for a thin endometrium [23].

Kaser et al. [22] reported that a thin endometrium was a risk factor for PAS in pregnancies conceived after ART (PAS [8.8 mm] vs. non-PAS [10.4 mm]). Additionally, in patients with PAS, EmT in the FET group was significantly thinner than that in the fresh ET group (FET [8.4 mm] vs. fresh ET [10.6 mm]), which was similar to that in patients without PAS (10.4 mm). Therefore, the pathogenesis of PAS may be different between fresh ET and FET. Our study included women who conceived after FET in an HRC, and we found that a thin endometrium in women with <2 previous uterine surgeries was another risk factor for PAS. This finding is consistent with that by Kaser et al. [22].

In Kaser et al.'s study [22], a thin endometrium and PAS were associated with low serum peak oestradiol concentrations. However, we found that serum oestradiol concentrations were not associated with the risk of PAS, and that there was no relationship between EmT and oestradiol concentrations in patients with PAS. There are two possible reasons for these discrepancies between Kaser et al.'s study [22] and our study. First, there were differences in the subjects between studies. In Kaser et al.'s study [22], approximately 80 % of all patients with ET had fresh ET in which endogenous oestrogen secretion and the oestrogen response to follicular stimulation were higher than those in women with FET. Second, there were differences in the route of exogenous oestradiol administration for endometrial preparation between the studies (82 % of women in Kaser et al.'s study had oral administration vs. 95 % who had transdermal administration in our study). Moreover, EmT and peak serum oestrogen concentrations are not correlated with each other [24], but related to oestrogen receptor expression in endometrial cells [25].

Ishihara et al. [26] reported that the incidence of PAS was not different between pregnancy after cleaved embryo transfer and that after blastocyst transfer. Additionally, the difference in the stage of embryo transferred (i.e., cleaved embryo or blastocyst) was not associated with the occurrence of PAS. In their report, the incidence of PAS (0.2 %) was much lower than that in our study (7.0 %) and that in other reports (1.2 %–24.1 %) [13], which resulted in a low statistical power. The inconsistency in the incidence of PAS is derived from differences in study populations and the diagnostic criteria of PAS. Although Ishihara et al.'s report [26] was based on a large number of subjects (i.e., national registry database from 2008 to 2010), the diagnostic criteria of PAS were unclear. In contrast, the sample size in our study was relatively small, with 972 women with pregnancy after ART. Additionally, PAS was diagnosed according to clinical and histological criteria on the basis of the FIGO classification [14].

This study showed that blastocyst transfer was associated with a higher risk of PAS than cleavage-stage embryo transfer. Blastocyst transfer requires a longer culture time for fertilised embryos under non-physiological conditions. Furthermore, cellular metabolism related to energy generation undergoes considerable changes in fertilised embryos during morula compaction and blastocyst formation, resulting in a substantial increase in oxygen consumption [27,28]. Consequently, *in vitro* cultured blastocysts are exposed to excessive oxidative stress. These circumstances can potentially affect the epigenome [29]. In fact, several

animal studies, which predominantly used mouse embryos, have demonstrated that blastocysts show greater epigenomic disturbance than cleavage-stage embryos [30–32]. These disturbances are believed to contribute to obstetric complications associated with ART, such as hypertensive disorders of pregnancy [33,34]. Specifically, DNA methylation plays a crucial role in the normal development of extra-embryonic tissues, particularly in the behaviour of trophoblastic cells and their invasive properties. Therefore, the functional mechanisms of extravillous trophoblasts may be partly regulated by epigenetic factors. However, the precise mechanism of epigenomic changes in human embryos related to the pathogenesis of PAS remains unclear. Further research is required to determine whether the incidence of PAS is higher in blastocysts with a longer culture time than cleavage-stage embryos, and whether this can be explained by epigenomic disturbances.

Immune cells such as natural killer (NK) and T cells, especially decidual NK cells, play a pivotal role in implantation [35]. Their interaction can trigger proinflammatory or tolerogenic effects, which are essential for maintaining immune balance at the maternal–foetal interface. Non-physiological hormonal conditions in ART can lead to abnormalities of decidual NK cells [36]. Dysregulated decidual NK cells are associated with pregnancy complications, such as hypertensive disorders of pregnancy [37]. Whether altered decidual NK cells are associated with PAS with FET in an HRC needs to be determined in future studies.

A strength of this study is that it is the first to examine the risk factors for PAS in women with FET in an HRC in detail. However, this study also has some limitations. First, the study design was retrospective, and the number of patients was limited. Second, the protocols of ART, including ovarian stimulation methods and drug type and quantity, were not standardised among the ART clinics. Additionally, procedures of an embryo biopsy and assisted hatching could not be considered in this study. However, there does not appear to be any evidence to suggest that these procedures are associated with PAS [38,39]. Third, our study period was over 11 years during which various techniques of ART would have improved, which may be a possible source of bias. However, because the incidence of PAS was relatively low, a long study span was inevitable for accumulating a sufficient number of patients, which was a prerequisite for conducting longitudinal data analyses by using a mixed-effect model. Further large-scale, prospective studies are warranted in the future to clarify the relationship between ART including FET in an HRC and PAS.

Conclusions

Multiple uterine surgeries, the transfer of blastocysts, and a thin endometrium before ET in patients with <2 previous uterine surgeries are risk factors for PAS in pregnancies conceived after FET in an HRC.

CRediT authorship contribution statement

Tomoyuki Fujita: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Toshiyuki Yoshizato:** Conceptualization, Writing – review & editing, Methology, Supervision. **Hiroshi Mitao:** Investigation. **Takuya Shimomura:** Investigation, Resources. **Takeshi Kuramoto:** Investigation. **Hitoshi Obara:** Formal analysis, Methodology, Software. **Hiroshi Ide:** Investigation. **Fumitoshi Koga:** Investigation. **Kayoko Kojima:** Investigation. **Mari Nomiyama:** Investigation. **Mayumi Fukagawa:** Investigation. **Yumi Nagata:** Investigation. **Atsushi Tanaka:** Investigation. **Hiroyuki Yuki:** Investigation. **Takafumi Utsunomiya:** Investigation. **Hidehiko Matsubayashi:** Investigation. **Chikahiro Oka:** Investigation. **Kohji Yano:** Investigation. **Masahide Shiotani:** Investigation. **Masaru Fukuda:** Investigation. **Hiromi Hirai:** Investigation. **Tatsuyuki Kakuma:** Writing – review & editing, Formal analysis, Methology. **Kimio Ushijima:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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