Acta Biomed 2023; Vol. 94, N. 3: e2023152 DOI: 10.23750/abm.v94i3.14437

Review

Endometrial thickness and live birth rates after IVF: a systematic review

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Abstract. *Aim:* This study aims to systematically review the current literature on published studies with data on the clinical significance of endometrial thickness on ultrasound for live birth rate (LBR) after in vitro fertilization (IVF) procedures. *Methods:* A comprehensive systematic review of PubMed, Web of Science, ScienceDirect, Google Scholar, and Open Gray databases and a subsequent hand search of the reference list of included studies was performed. *Results:* We found 20 eligible studies that evaluated 20 546 patients for endometrial thickness, presented risk factors for decreased endometrial receptivity, and IVF outcomes with fresh and frozen embryo transfer (FET) cycles. The mean age of the patients ranged from 28.86 to 41.03 years. Reported endometrial thickness ranged from <4 mm to >15 mm. The clinical pregnancy rate varied from 9,09% to 61,49% in fresh embryo transfer cycles and from 13,3% to 79,31% in FET cycles. Overall, LBR varied between 4,80% and 48,99% in fresh embryo cycles and between 6.06% and 39,19% in FET cycles. Limitations. Only English-language studies were included; most studies were from the China region; retrospective study design used in most studies; different ET thresholds, which in turn could significantly alter the correlation with pregnancy outcomes; different IVF procedure protocols in fresh or FET cycles. *Conclusions:* IVF outcomes in patients with impaired endometrial receptivity do not depend only on the condition of the endometrium. Risk factors and endometrial thickness significantly affect LBR in fresh and FET cycles. (www.actabiomedica.it)

Key words: endometrial thickness, IVF, ICSI, live birth rate, systematic review

Introduction

There are many factors that influence the success of assisted reproductive technology (ART) programs, including maternal age, endometrial characteristics such as endometrial structure, endometrial thickness (ET), subendometrial blood flow, and the number of embryos available for transfer (1–3). While routine monitoring of ET during ovarian stimulation is not recommended, it can be measured by ultrasound examination during oocyte aspiration or on trigger day to detect a very thin endometrium that may affect the outcome of ART procedures (4).

Over the years, there have been numerous publications on potential sonographic markers of endometrial receptivity (5). Although it remains controversial,

ET is the most commonly used predictor of endometrial receptivity and live birth rate (LBR) in ART programs such as in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (1,6,7). Decreased endometrial receptivity is associated with decreased likelihood of pregnancy, spontaneous miscarriage, ectopic pregnancy, low birth weight, and low birth weight relative to gestational age (8,9).

Pregnancy outcome data were similar in fresh and frozen cycles, including rates of clinical pregnancy, implantation, and fertility (10,11). Nevertheless, ET was a better predictor of endometrial receptivity in fresh in vitro fertilization (IVF) cycles than ET in frozen embryo transfer (FET) cycles (12,13).

The most common factors for thin endometrium (up to 60%) have been associated with intrauterine surgery, which can damage the basal layer of the endometrium (14,15). In some women, the endometrium may also be thin in nature (16) or under the influence of steroid hormones (17). Transcriptome analysis can predict a thin endometrium by identifying genes with increased activity (18).

The authors of this study found no published articles comparing clinical and epidemiological factors that might be associated with LBR in patients who went through fresh and FET cycles with thin endometrium. This study aims to systematically review the current literature on published studies with data on the clinical and epidemiological data of the patients with thin endometrium who underwent fresh and FET cycles to compare their LBR and possible risk factors.

Materials and methods

The study protocol is registered with the PROSPERO International prospective register of systematic reviews (ID: CRD42022359149).

Search strategy

The PROSPERO database was searched to identify the registry of studies that evaluated EMT and outcome after IVF treatment, and no similar studies were found. Therefore, the PubMed, Web of Science, ScienceDirect, Google Scholar, and Open Grey databases were searched between July 2022 and October 2022 for this review. The full search strategy for the databases is provided in the supplementary materials. After the initial selection of the studies from the database search, we performed a hand search of the literature based on the list of references of the selected articles from the database search.

Eligibility criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) methods were used in this review. Inclusion criteria for studies were: 1) cohort studies or randomized clinical trials; 2) included subfertile childbearing women undergoing IVF or ICSI (aged ≥18 years); 3) endometrial thickness was measured by transvaginal ultrasound; 4) reported either the proportion or number of patients with outcomes of interest: Live birth rates and clinical/epidemiological data of the patients; 5) were published in English from January 2014 to October 2022. The exclusion criteria: 1) publications that lacked the required information; 2) publications that repeated previously reported study results; 3) had a high risk of bias; 4) donor oocytes were used in the study.

Study selection and data extraction

Database searches, selection of studies based on their inclusion/exclusion criteria, and data extraction were performed by two independent researchers (IK and GM) according to PRISMA guidelines (19). The authors were contacted by email up two times to obtain missing data. The list of required information was prepared and approved by all authors and included: first author, year, country, study design, setting, transfer of fresh or frozen oocytes, prevalence of patients with thin endometrium, factors associated with thin endometrium, LBR, ET in millimeters.

The electronic databases Pubmed, Web of Science, ScienceDirect, Scopus, and Google Scholar were searched between July 2022 and October 2022 for articles describing EMT and LBR after IVF treatment. The search strategy included the following keywords: “thin endometrium IVF”; “thin endometrium invitro fertilization”; “thin endometrium pregnancy”; “thin endometrium

live birth". Search results were restricted using filters to publications published between 2014 and 2022. No restrictions were applied to the type of publication.

The titles and abstracts of all identified studies were screened, and the full texts of the initially selected articles were read by two researchers (G.M. & I.K.). Both researchers independently extracted data from the full texts of the articles using a prepared data extraction form. A narrative review was conducted to summarize the results.

Risk of bias assessment

According to the Cochrane Collaboration Network Risk Assessment Tool, biases include selection bias, performance bias, discovery bias, attrition (discontinuation) bias, and reporting bias (20). A bias risk assessment was performed independently by each of the two reviewers. When this was not possible, a discussion was held with the third author. The following assessments were used: low risk, high risk, or unclear (lack of information or uncertainty regarding the potential for bias).

Results

A comprehensive search of Pubmed, Web of Science, ScienceDirect, Scopus and Google Scholar found 1939 nonduplicative titles. Further screening for relevant articles based on title and abstract yielded 837 records. 81 full-text articles were screened for eligibility, and 20 articles were included in the systematic review. The flowchart of study selection is shown in Figure 1.

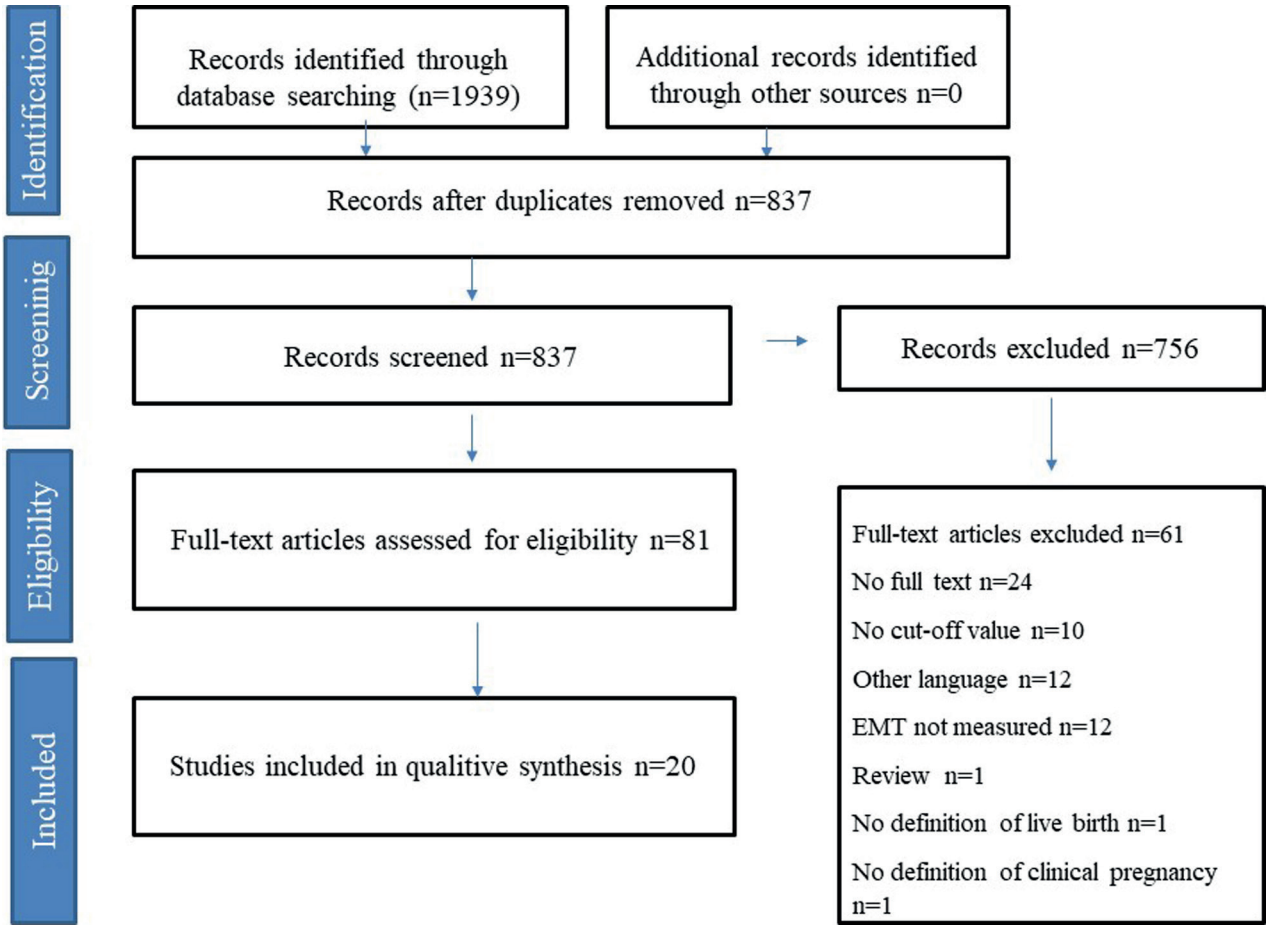

Figure 1. The flowchart of study selection.

Methods of the studies

The study design and characteristics of patients with thin endometrium are presented in Table 1. Most of the studies were conducted in China (eleven). We also included studies from Turkey (35), Portugal (25,38), Argentina(34), Israel (32), Switzerland (26), Canada (37), South Korea (27), the United Kingdom (2), and India (36). Seven studies were retrospective cohort studies, seven studies were retrospective, two studies were prospective-interventional, two studies were prospective, one study was longitudinal-experimental, and one study was prospective-interventional. Six studies reported fresh embryo transfers and 11 studies reported frozen embryo transfers. Three studies reported both fresh and frozen embryo transfers. All studies had a low risk of bias.

Subjects

A total of 14 804 patients were included in 20 studies (mean sample size = 306 patients, range = 24 to 3350 patients). The mean age of the subjects ranged from 28.86 to 41.03 years. The mean BMI of the patients ranged from 20.93±0.97 to 26.2±2.7. Reported ET rates ranged from <4 mm to >15 mm. Clinical pregnancy rates ranged from 9.1% to 79.3%, and live birth rates ranged from 4.8% to 48.99%. In the different studies, ET was measured at different time points. ET was most commonly measured on the day of human Chorionic Gonadotropin (hCG) administration regardless of the embryo transfer setting (Fresh or FET).

Live birth rate in fresh and frozen embryo transfer cycles and associated risk factors

LBR ranged from 4.80% to 48.99% in fresh embryo cycles, and from 6.06% to 39.19% in FET cycles overall. Clinical pregnancy rates ranged from 9.09% to 61.49% in fresh embryo transfer cycles, and from 13.3% to 79.31% in FET cycles. In five of nine studies reporting Fresh cycles, the LBR was less than 20%. In all those five studies the CPR was less than 30%. In six of fourteen studies reporting FET cycles the LBR was less than 20%. There was only one study with a CPR above 30%. In the study with the lowest percentage of live births during fresh cycles, the mean age of the patients was 29.5 + 3.2 years, whereas the mean duration of infertility was relatively short – 3 years. In the study with the lowest percentage of live births during the FET cycles, most patients were 20.93±0.97 years on average.

The risk factors and LBR reported by the studies are summarized in Table 2. The full table with risk factors is presented in Supplemental Table 1.

Discussion

IVF outcomes related to the thickness of the endometrium remain an urgent problem in the field of reproductive medicine. Inadequate endometrial receptivity accounts for two-thirds of failed implantations, while only one-third of failures depend on embryo quality(39). In a meta-analysis by Kasius et al. (1) the rate of clinical pregnancy was found to be lower when the ET is <7.0 mm, at the same time it was not associated with the rate of sustained pregnancy and live birth. A meta-analysis by Gao et al. (40) examined the significant role of ET in pregnancy outcomes after IVF. The results of this study showed that women with lower ET had lower pregnancy and live birth rates than women with higher thickness, regardless of whether a fresh or frozen cycle was performed. In the study by Mahutte et al. (9) an increase in live births was also observed in fresh embryo transfer cycles with an increase in ET up to 10-12 mm, and in frozen cycles, LBR increased after 7-10 mm. According to a study by Liu et al. (41) rates of clinical pregnancy and live births decrease with each millimeter ET for fresh IVF cycles below 8 mm, and for FET IVF cycles below 7 mm. However, in this review, we see that there are studies in which rates for clinical pregnancies and live births remain quite relevant in patients with an ET of 4 to 6 mm.

Analysis of the study showed that the relationship between ET and LBR, in patients who underwent a fresh or FET cycle depended on study design, ET thresholds, significant risk factors such as age, BMI, type of infertility, reproductive loss history, surgical interventions in the cavity of the small pelvis,

Table 1. Characteristics of the included studies.

#	First author, year, country	N	Age, years mean±SD or mediana	BMI (kg/m2) mean±SD or mediana	Setting & When ET was measured	ET	CPR	LBR
1	Xu et al., (21) 2015, China	82	31.4 ± 4.0	21.8 ± 2.5	FET: G-CSF group: daily or every other day after G-CSF perfusion	<7	48.2%	33.3%
			32.0 ± 3.9	21.5 ± 3.0	FET: No treatment group: administration of progesterone or hCG	<7	25.0%	17.3%
2	Bu et al., (2) 2016, United Kingdom	2997	31.8±4.8	22.6±3.3	FET: Morning on the day of embryo transfer.	<7	33.4%	23.8%
3	Yuan et al., (8). 2016, China	521	29.5 + 3.2	21.5 + 3.7	Fresh: hCG administration	<8	23.00%	15.0%
4	Kunicki et al., (22)2017, China	134	N/A	23.5±3.9	FET: G-CSF group: Thin unresponsive endometrium in previous cycles	<7	17.2%	6.9%
			N/A	20.9±0.9	FET: No treatment group: Thin unresponsive endometrium in previous cycles		15.2%	6.1%
5	Zheng et al., (23) 2017, China	571	31.5±3.9	21.5±2.7	FET: hCG administration	<10	48.2%	39.2%
			31.6± 4.2	21.9±2.6	FET: Twice cryopreserved group: hCG administration		44.1%	29.1%
6	Ke et al., (24) 2018, China	226	32.0 (28.8-36.0)	22.9 (20.7-25.9)	FET: Measurements were repeated at least 3 times and the mean value was recorded.	<7	33.3%	12.8%
7	Ribeiro et al.,(25) 2018, Portugal	3350	33 (31–36)	22.5 (20.4–26.4)	FET: hCG administration	<7	28.9%	21.8%
8	Von Wolff et al, (26) 2018, Switzerland	106	29.5 + 3.2	21.5 + 3.7	Fresh: Oocyte retrieval	<7	9.5%	4.8%
9	Zhang et al., (12) 2018, China	1512	30.3±4.2	21.5±5.8	Fresh: oocyte retrieval	<6	50.0%	33.3%
					FET: progesterone supplementation		34.8%	26.1%
10	Kim et al., (27) 2019, South Korea	24	22.5 (20.4–26.4)	23.3±3.1	FET: Three days after the final autologous PRP administration	<7	20.0%	20.0%
11	Song et al., (28) 2019, China	624	28.9 ±3.2	21.3 ± 3.5	Fresh: Short GnRH-a group: hCG administration.	<7	9.1%	9.1%
			29.5 ± 3.2	21.5 ±3.7	Fresh: Prolonged GnRH-a group: hCG administration.		36.0%	28.0%
12	Bu et al., (29) 2020, China	309	36.8 ±3.8		FET: hCG administration	<7	n/a	35.5%
13	Guo et al., (30) 2020, China	1110	34.8±5.5	23.8±3.6	Fresh: hCG administration or	<7	26.4%	18.4%
			33.6±5.4	23.3±3.5	FET: administration of progesterone		40.0%	31.0%
14	Mao et al., (31) 2020, China	302	37.8 ± 5.4	22.0±2.8	FET: GM-CSF group: administration of progesterone	<7	28.6%	19.5%
			37.0 ± 4.9	21.7 ± 2.8	FET: No treatment group: administration of progesterone		13.3%	9.5%

(*Continued*)

#	First author, year, country	N	Age, years mean±SD or mediana	BMI (kg/m2) mean±SD or mediana	Setting & When ET was measured	ET	CPR	LBR
15	Simeonov et al., (32) 2020, Israel	2114	37.1 ± 4.5		Fresh: hCG administration	<6	19.9%	11.2%
16	Song et al., (33) 2020, China	302	31.3±4.0	22.0±3.0	Fresh: Prolonged GnRH-a group: hCG administration	<8	43.9%	36.5%
			31.1±4.8	22.2±2.9	Fresh: Short GnRH-a group: hCG administration		28.6%	20.8%
17	Tersoglio et al., (34) 2020, Argentina	29	41.7±5.2	24.8±5.1	FET: The day of luteinizing hormone	<7	79.3%	34.5%
18	Yurci et al., (35) 2021, Turkey	380	28.9±4.8	26.2±2.7	Fresh: hCG administration	<15	61.5%	49.0%
19	Dogra et al., (36) 2022, India	26	32.4±3.9	25.6±4.1	Fresh: Day 8	<7	25.0%	33.3%
					FET: Day 8		25.0%	9.1%
20	Russell et al., (37) 2022, Canada	85	38.0 ± 5.3	23.5 ± 4.3	FET: Every 3–4 days prior to each PRP infusion until the lining reached the target thickness.	<7	21.8%	14.6%

Abbreviations: BMI - body mass index; CPR – clinical pregnancy rate; ET – endometrial thickness; FET – frozen embryo transfer; hCG - human chorionic gonadotropin; LBR – live birth rate; N – number; PRP – platelet-rich TE – thin endometrium

Table 2. Risk factors associated with thin endometrium.

Fresh Cycles					
Live birth rate	**Clinical pregnancy rate**	**Cause of infertility**	**Duration of infertility, yrs, mean±SD or median (range)**	**Secondary infertility**	**First author**
LBR>20%	CPR >30%	Tubal factor 31.5% Male factor 21.4% Endometriosis 5.8% PGD - chromosomal abnormality 1.7% PGD - thalassemia of both partners 1.3% Multiple factors 35.2% Unexplained infertility 3.1%	4.0 (1.0–20.0)		Yuan et al., (8) 2016
		Severe male factor 25.9% Moderate/mild male factor 22.2% Tubal factor, endometriosis rAFS I-II. and Mixed factors 18.5% Idiopathic 33.3%	3.0 (2.0-4.0)		Von Wolff et al., (26) 2018
		Progesterone levels on trigger day <1.5 ng/mL	3.9 + 2.1	34.9%	Song et al., (28) 2019 (Fresh Short GnRH-a group)
		PCOS, n (%) 9.5%	4.1±3.2		Guo et al., (30) 2020
		Male 27.88% Other 72.12%		61.9%	Simeonov et al., (32) 2020

FET cycles					
Live birth ateBR	**Clinical pregnancy rate**	**Cause of infertility**	**Duration of infertility**	**Sec-ondary infertility**	**First author**
LBR<20%	CPR <30%	Surgical abortion/evacuation 1.1 ± 1.6	5.5 ± 3.8	67.3%	Xu et al., (21) 2015 (control)
		Tubal factor 10.34% Male factor 27.59% PCOS 6.90% Other 6.90% Unexplained 37.93% Mixed 10.34%		41.4%	Kunicki et al., (22) 2017 (G-CSF group)
		Tubal factor 9.09% Male factor 24.24% Endometriosis 6.06% PCOS 0% Other 6.06% Unexplained 39.39% Mixed 15,5%		39.4%	Kunicki et al., (22) 2017 (control group)
		Tubal factor 31.68% Other female factors 11.18% Male factors 6.83% Mixed factors 49.69% Unknown factors 0.62%	5.0 ± 3.3	79.5%	Mao et al., (31) 2020 (GM-CSF group)
		Tubal factor 30.07% Other female factors 5.59% Male factors 4.90% Mixed factors 59.44% Unknown factors 0%	3.9 ± 2.6	69.9%	Mao et al., (31) 2020 (control group)
		Infertility not related to endo-metrial changes on hysteroscopy 100%	7.9±4.6		Dogra et al., (36) 2022
		Poor ovarian reserve 51.35% Repeat pregnancy loss 21.62% Advanced reproductive age 29.73% Asherman's 10.81% Fibroids 10.81% Other diagnoses 27.03%	2.0 ± 2.0		Russell et al., (37) 2022
	CPR >30%	Pelvic/tubal factor 78.65% Endometriosis 9.74% Male factor 4.42% PCOS 24.78% Unexplained 1.32% Intrauteine adhesion15.04% Uterine curettage 62.39%	3.0 (2.0-5.0)		Ke et al., (24) 2018

Abbreviations: CPR – clinical pregnancy rate; ET – endometrial thickness; FET – frozen embryo transfer; FSH - follicle-stimulating hormone; G-CSF - granulocyte colony stimulating factor; GnRH-a - gonadotrophin releasing hormone agonist; hCG - human chorionic gonadotropin; LBR – live birth rate; N – number; PCOS - polycystic ovary syndrome; PGD - preimplantation genetic diagnosis; SD – standard deviation.

ineffectiveness of IVF programs, hormonal profile including initial level of follicle-stimulating hormone (FSH) in blood serum, and ovulatory reserve. Possible reasons and limitations of the present study: only English-language studies were included; most studies were from the China region; retrospective study design was used in most studies; different ET thresholds, which in turn could significantly alter the correlation with pregnancy outcomes; different IVF procedure protocols in fresh or FET cycles.

There are many studies in the databases, and many conflicting results, but a variety of risk factors have shown that ET can be used as a predictor of pregnancy and live birth in fresh or frozen cycles. Among risk factors for thin endometrium, a history of recurrent reproductive losses associated with surgical abortions, endometriosis in women with secondary infertility, as well as tubal factors of infertility have drawn attention.

Conclusions

IVF outcomes in patients with impaired endometrial receptivity depend not only on the state of the endometrium. Risk factors and ET significantly affect LBR in Fresh and FET cycles. According to the results of the systematic review, in women with impaired endometrial receptivity, it is important to apply a personalized approach with high-quality diagnostics and effective treatment methods to achieve adequate thickness with improved endometrial receptivity. Due to the methodological weaknesses of the included studies, further research is needed to evaluate the independent importance of ET, structure, treatment protocols and other factors.

Acknowledgments: The authors thank Dr. Sandugash Yerkenova and the group of experts who participated in the review and analysis of the data.

Funding Statement: This research is funded by Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grant no. AP 14870089).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Human and Animal Rights: This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Ethical Statement: This study was approved by the Local Ethics Committee of Kazakhstan Medical University "KSPH" (study ID: 04-09-86717; date: 28/08/2022) with the exemption of informed consent.

Authors Contribution: GM: Conceptualization, Methodology, Investigation, Writing – Original /draft preparation. IK: Investigation, Formal Analysis, Writing – Original /draft preparation, Writing - Review and Editing. AK: Supervision. NM: Data curation, Project Administration. AA: Resources, AM & ZY: Validation. BZ: Software..

Availability of Data: Data of this study is available upon request.

Study Registration: The study protocol was registered with the ClinicalTrials.gov Protocol Registration and Results System (reference: NCT05427994).

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Received: 11 March 2023
Accepted: 26 April 2023
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