The safety of time-lapse incubation system for embryo culture in assisted reproductive laboratory: A systematic review and meta-analysis

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Abstract

Background: To date, time-lapse incubation system (TLI) is widely used in assisted reproductive laboratory for continuously embryo observe and selection. But only few randomized controlled trials (RCT) have been published that evaluated the safety of TLI, especially the neonatal outcomes. We conducted a systematic review and meta-analyses to evaluate the neonatal outcomes between TLI and standard incubators (SI).

Methods: A literature search up to October 2021 was carried out to search for clinical trials from electronic databases comparing TLI versus SI on neonatal outcomes. The summary measures were reported as odds ratio (OR) with 95% confidence-interval (CI).

Results: A total of 5905 live-born infants were included from fresh embryos transfer cycles. Only singleton pregnancies were analyzed, no statistical differences were found with respect to gestational weeks at delivery (Mean difference=0.09; 95%CI, -0.18 to 0.35; I^2=33%; *P*=0.52), preterm births (<37weeks) (OR=0.98; 95%CI 0.78 to 1.24; I^2=0%; *P*=0.86), and early preterm birth (<32 weeks) (OR=0.41; 95%CI, 0.11 to 1.50; I^2=50%; *P*=0.18). Besides, no statistical significances were also observed in TLI group on birth weight (Mean difference=71.61; 95%CI, -30.55 to 173.77; I^2=62%; *P*=0.17), low birth weight rate (<2,500g) (OR=0.85; 95%CI, 0.64 to 1.13; I^2=0%; *P*=0.26), very low birth weight rate (<1,500g) (OR=0.58; 95%CI, 0.17 to 1.96; I^2=50%; *P*=0.38), and macrosomia rate (≥4,000g) (OR=1.11; 95%CI, 0.84 to 1.47; I^2=0%; *P*=0.48). Moreover, incidences of malformations of babies delivered from TLI and SI groups were also similar (OR=1.19; 95%CI, 0.66 to 2.14; I^2=0%; *P*=0.56). And finally, sex ratio analysis still showed no differences between the two groups (OR=2.16; 95%CI, 0.53 to 8.81; I^2=96%; *P*=0.28).

Conclusions: The strategy of culturing embryo in time-lapse incubation systems would not increase adverse risks of neonatal outcomes comparing to SI.

Trial registration: PROSPERO (2018: CRD42020186807)

Introduction

In recent years, the methods of non-invasive embryo evaluation and selection have been greatly developed. One of these methods coming into the limelight is the time-lapse incubation systems [1–3]. It has been widely used in clinical practice for the continuous monitoring of human embryos and provided more information on embryo morphokinetics compared to standard culture incubators [4, 5].

Time-lapse incubation systems offer at least two advantages over conventional culture methods: (a) it does not need to be taken out from the incubator for observation, therefore, perturbations to embryo culture environment were minimized [6, 7]. (b) it allows development of algorithms based on the extensive morphokinetic markers which may facilitate selection of viable embryos for transfer [8–10].

Currently, it remains a controversial subject whether TLI is superior to conventional methods for human embryo incubation and clinical outcomes. However, several studies showed that such morphokinetic enhanced embryos selection method and “undisturbed” culture may help to identify embryos with high implantation potential to increase clinical outcome [11–14].

However, concerns have been raised regarding the safety of the time-lapse incubator, considering the more frequent exposure to light during the image acquisition. It has been reported that considerable light exposure may be detrimental to embryo development [15]. Furthermore, risk to embryo development may be raised by the presence of magnetic fields, the warmth created by moving parts, and the presence of lubricants inside the instrument near the culture dish [16].

Although several studies have provided reassurance that TLI does not have a detrimental effect on embryo development, implantation potential, and clinical pregnancy rates, there is still insufficient evidence regarding the impact of TLI on obstetric and perinatal outcomes [17, 18].

Hence, for the purpose of evaluating the safety of TLI technique, we performed this meta-analysis to compare the neonatal outcomes of pregnancies resulting from embryos conceived in TLI and standard incubators. To our knowledge, this is the first systematic review and meta-analysis on this topic.

Methods

We registered this review in the international prospective register of systematic reviews (PROSPERO, registration number CRD42020186807).

Data sources and search strategy

Three reviewers independently identified the relevant articles by searching the PubMed, EMBASE, Cochrane library, ClinicalTrial.gov and BioMed Central databases up to October 2021. The following search terms and keywords were used: (“time-lapse” OR “time lapse” OR EmbryoScope OR “EEVA” OR “Primo Vision” OR “live cell imaging”) AND (“perinatal outcome” or “neonatal outcome”). No publication date, study design, or publication status restrictions were imposed.

Eligibility criteria and study selection

Three reviewers independently screened trial eligibility on the basis of titles, abstracts, and full-text publications. Potential articles had to satisfy the following eligibility criteria: (i) comparative studies including randomized and non-randomized controlled trials (NCTs), observational cohort studies and case-control studies; (ii) human studies; (iii) availability of obstetric and perinatal outcome data. Discrepancies were solved by group discussion. We contacted the original authors by e-mail when necessary.

Data extraction and quality assessment

Three reviewing authors independently extracted quantitative and qualitative data by using a standard data extraction form. For RCTs, the same investigators independently and systematically assessed the studies' methodological quality using the Cochrane tool for risk of bias assessment [19]. For NCTs and observational studies, the Newcastle-Ottawa Scale (NOS) tool was used to evaluate items considered relevant to this review topic [20]. Any disagreement was resolved through discussion. Funnel plots were used to screen for potential publication bias.

Data synthesis and data analysis

Outcome measures

The neonatal outcomes included gestational weeks at delivery, birth weight (BW), sex ratio, and the risk of preterm births (PTB, <37weeks), early preterm births (early PTB, <32weeks), low birth weight (LBW, <2,500g), very low birth weight (VLBW, <1,500g), macrosomia (≥4,000g), and congenital malformations.

Statistical analysis

For dichotomous outcomes, the odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to assess the overall effects. All meta-analysis were conducted with Review Manager Version 5.3 (Cochrane Collaboration, Software Update, Oxford, United Kingdom, 2014) in a random-effect model or the fixed-effect model. Statistical heterogeneity among the study results was examined by the *P* value and I^2 statistic. Statistical significance was set at a *P* values<0.05.When the clinical and methodological heterogeneity was greater than 40% (I^2>40%), we applied the random-effects model.

Results

Search results

After removal of 70 duplicates, a total of 216 citations were hit. We excluded 206 articles by reviewing titles and abstracts as they were considered non-relevant screened. We retrieved a further two articles through hand-searching. Therefore, 10 remaining studies were selected to undergo further full-text review. Among these studies, 5 were excluded for absence of quantitative data. In total, we included a total of two RCTs and three Retrospective cohort studies involving 5905 live-born infants in the quantitative synthesis. Study selection process is shown in PRISMA flow diagram (**Fig.1**).

Study characteristics and bias assessment

Five studies assessing neonatal outcomes of singleton pregnancies after TLI versus SI meeting the inclusion criteria. Studies were conducted in various regions including Hungary, Spain, America, England and China. Both in vitro fertilization (IVF) or intra cytoplasmic sperm injection (ICSI) cycles were performed in TLI and standard culture groups in our study. Further, both day 3 embryos and blastocysts transferred were included in our meta-analysis. The age of patients and mature oocytes might lead to bias in the results, so in one of our included studies [21], we only selected data matched the ages and oocytes of the TLI group. Among the 3 eligible retrospective cohort studies, we use NOS for quality assessment. The main trial and patient characteristics of the included studies were summarized in **Table 1**. Finally, **Fig.6** showed a funnel plot of four studies included in this meta-analysis that reported low birth weight. All studies lay inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias.

Main outcomes

Gestational weeks at delivery

There were four studies analyzing gestational weeks at delivery in singleton pregnancies between TLI group and SI group, including 2399 live births in the TLI group, and 1845 live births in the SI group and no significant difference was observed (Mean difference=0.09; 95%CI, -0.18 to 0.35; I^2=33%; *P*=0.52; n_{TLI}=2399, n_{SI}=1845; **Fig.2A**).

Preterm birth (PTB, <37 weeks)

Four studies (two RCTs and two retrospective cohort studies) reported PTB, including 2399 live births in the TLI incubation group, and 1845 live births in the SI group. There were no significant differences between the two groups with the overall odds ratio (OR) for preterm birth was 0.98 (95%CI, 0.78 to 1.24; I^2=0%; *P*=0.86; n_{TLI}=2399, n_{SI}=1845; **Fig.2B**).

Early preterm birth (early PTB, <32 weeks)

Two RCTs and two retrospective cohort studies reported early PTB, but a RCT (Insua et al. [22]) was excluded for its early PTB was defined as before 34 gestational weeks, not fulfilled our criteria which was defined as before 32 weeks. In total, 2250 singleton live births were included in the TLI incubation group and 1723 singleton live births in the SI group. There were also no significant differences between the two groups (OR=0.41; 95%CI, 0.11 to 1.50; I^2=50%; *P*=0.18; n_{TLI}=2250, n_{SI}=1723; **Fig.2C**).

Live birth weight

Four studies (Bingxin et al. [21] Kovacs et al. [2]; Insua et al. [22]; Mascarenhas et al. [23]) were included for meta-analysis to investigate overall impact on the singleton live birth weight (BW), low birth weight (LBW, <2,500g), and very low birth weight (VLBW, <1,500g). Overall, our meta-analysis included 2399 live

births in the TLI group, and 1845 in the SI group. The results showed no significant differences on birth weight in TLI group comparing to standard group (Mean difference=71.61; 95%CI, -30.55 to 173.77; I^2=62%; *P*=0.17; n_{TLI}=2399, n_{SI}=1845; **Fig.3A**).

Low birth weight (<2,500g)

Four studies reported low birth weight, including 2399 singleton live births in the TLI group, and 1845 singleton live births in the SI group. The overall OR was of 0.85 (OR=0.85; 95%CI, 0.64 to 1.13; I^2=0%; *P*=0.26; **Fig.3B**) when comparing LBW rate between different groups. Our result showed that TLI group would not increase risks of LBW compared with SI group in fresh ET (Embryo transfer, ET) cycles.

Very low birth weight (<1,500g)

4244 babies were reported about VLBW, including 2399 in the TLI group, and 1845 in the SI group. But no significant difference was observed between the TLI group and the SI group in fresh cycles (OR=0.58; 95%CI, 0.17 to 1.96; I^2=50%; *P*=0.38, n_{TLI}=2399, n_{SI}=1845; **Fig.3C**). The results of fresh ET cycles indicated that TLI group would not increase the risk of VLBW rate.

Macrosomia (≥4,000g)

As for macrosomia rate, only two studies involving 3913 live-born infants were included. Our meta-analysis showed that TLI group would not increase risks of macrosomia rate compared with SI group in fresh ET cycles (OR=1.11; 95%CI, 0.84 to 1.47; I^2=0%; *P*=0.48, n_{TLI}=2216, n_{SI}=1697; **Fig.4A**).

Malformations

With respect to the risk of congenital malformations, three studies involving 5252 live-born infants were included. We found no differences in incidence of congenital malformations between the TLI and SI groups (OR=1.19; 95%CI, 0.66 to 2.14; I^2=0%; *P*=0.56; n_{TLI}=2971, n_{SI}=2281; **Fig.4B**).

Sex ratio

Sex ratio analysis of newborn babies also showed that there was no difference between the two groups (OR=2.16; 95%CI, 0.53 to 8.81; I^2=96%; *P*=0.28; n_{TLI}=2024, n_{SI}=1567; **Fig.5**).

Discussion

To our knowledge this is the first and only one systematic review and meta-analysis to evaluate the neonatal outcomes after incubation in TLI vs. SI, and found no increased risk of abnormal events when comparing the two types of incubation.

Birth weight is associated with morbidity and mortality, therefore, it is commonly used for the assessment of neonatal outcomes [24]. In our meta-analysis, the mean birth weight of the TLI group was similar to the SI group without any significant differences (Fig. 3A). It is determined that birth weight was related to many factors. Firstly, birth weight increases with the increasing of gestational age, with an upward trend in the late stage of pregnancy. It tends to stabilize after 40 gestational weeks [25]. We only found four studies considering birth weight, but no significant difference was observed in gestational weeks at delivery between TLI group and SI group. Secondly, birth weight has been linked to infant gender, with boys having heavier birth weights than girls at every gestational age [25]. In our study, only two studies compared the gender ratio of the infants, and no significant differences were found (*P* = 0.28). Furthermore, birth weight is somewhat positively associated with maternal body mass index (BMI) [26], for the value of BMI was mainly represent maternal healthy and nutritional status. Of the four articles included in our meta-analysis, three had no statistical difference and one did not mention BMI. Since a higher birth weight was found in live-born infants with frozen ET cycles in comparison to fresh ET cycles [27, 28], we excluded frozen embryo transfer cycles. Actually, animal studies have shown that culture media constituents are responsible for changes in birthweight of offspring [29]. In human IVF, Nelissen et al. showed that the type of embryo culture medium had a significant effect on birthweight of the baby [30]. In contrast, Vergouw et al. demonstrated that there was no significant association between the type of embryo culture medium and birthweight adjusted for gestational age, gender and parity of singletons born after a fresh or frozen-thawed SET [31]. But in our four studies about birthweight included in meta-analysis, all embryos were cultured in sequential culture medium.

Low birth weight had been associated with neonatal morbidity, mortality and long term health outcomes [32, 33]. With regard to VLBW, it likely related to disease and treatment contributing to postnatal growth failure [34]. However, no clinically relevant neonatal risks were found in our analysis concerning LBW rate and VLBW rate (*P* > 0.05).

Infants born preterm are recognized to be at increased risk of many adverse health outcomes, leading to perinatal mortality and a considerable burden of complications [35]. While comparing preterm birth and early preterm birth rate, we did not find any significant differences between TLI and SI group, which indicated that culturing embryo in TLI would not increase risks of PTB and early PTB. Maybe, it was showed that blastocyst stage transfer was associated with an increased risk of preterm birth [36]. However, four studies in our analysis all transferred cleavage embryos and blastocysts.

When comparing the rate of congenital malformations, our study showed that TLI group would not increase risk of malformations. One of our included studies didn't make it clear whether birth defect rates were divided into singletons or twin pregnancies. As is well known, twins or multiple pregnancies in comparison to singletons, show a higher risk to have chromosomal disorders, prenatal death, prematurity, perinatal mortality, morbidity or other congenital malformations [37–39]. Moreover, the smaller twin significantly increase risks for malformations like patent ductus arteriosus, retinopathy of prematurity, and neurodevelopmental impairment [40]. Therefore, stable culture and the selection of single viable embryo for transfer by TLI technology are crucial in reducing multiple pregnancies [41]. What's more, only one trial with data on neonatal height, pregnancy-induced hypertension and Apgar score outcomes of

pregnancies conceived with embryos cultured in a time-lapse monitoring system has been published (Insua et al. [22]), no significant differences were found between the two groups.

Our review included significant sample sizes, 3346 singleton live births by TLI and 2559 by SI group. Therefore, this relatively large sample size will significantly increase the validity of our findings. Besides, to avoid bias and accurately examine the impact of TLI on neonatal outcomes, we only focused on newborns delivered from singleton pregnancies to reduce skewing of the data due to vanishing twins. Moreover, we also excluded frozen ET cycles in terms of BW, LBW, VLBW and macrosomia in our study.

Our study had some limitations. First, only five studies, two RCTs and three retrospective cohort studies, were included. Although several studies adjusted for confounding factors (including age and stage of the embryos transferred), other unknown confounding factors could be influencing the outcomes during this meta-analysis. What's more, Only ICSI patients (Insua et al. [22]) or only IVF patients (Zaninovic et al. [42]) were included, which may limit the generality of the results. In addition, some retrospective data were partially obtained through medical questionnaires or contacted patients again to clarify any inaccuracies whenever necessary. Furthermore, the baseline characteristics of singleton pregnancies in some retrospective data were not described separately, and vanishing twin pregnancies could have also influenced the results. Last but not the least, we should emphasize that studies included in our meta-analysis were all using the EmbryoScope systems. Therefore, our results could not generalize to the other different time-lapse incubation systems. Different time-lapse devices may bring different clinical results. There are at least three time-lapse incubation systems available in the IVF laboratory, including Primo Vision, EmbryoScope, and Eeva [18]. Each of them was designed with different parameters. For example, different light source, different ways of embryos are brought into the field of view, and different culture environment.

Conclusion

To sum up, our data indicated that TLI in assisted reproductive laboratory would not increase adverse risks on neonatal outcomes. However, further RCT studies with large sample size are definitely needed to draw a conclusion.

Abbreviations

TLI: Time-lapse incubation systems; SI: standard incubators; OR: Odds ratio; CI: confidence-interval; RCT: Randomized controlled trial; NCT: Non-randomized controlled trial; NOS: Newcastle-Ottawa Scale; BW: birth weight; PTB: preterm births; LBW: low birth weight; VLBW: very low birth weight; IVF: in vitro fertilization; ICSI: intra cytoplasmic sperm injection; BMI: body mass index; ET: Embryo transfer.

Declarations

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Authors' contributions

Design of the study: LYX; literature search and screening: LYX, SGH, and HGL; data extraction and risk of bias assessment: LYX, SGH and HGL; data analysis: LYX, SGH, HGL, WHH and CB; results visualization: LYX, SGH and HGL; manuscript draft and modification: LYX, SGH, HGL, WHH, CB, ZSH and XYW; funding acquirement: XYW. All authors reviewed and approved the final version of the manuscript.

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Table

Table 1: Description of included studies in the meta-analysis

Study and year	Country	Study design	Period of enrollment	TLI group, live births	SI group, live births	Type of ART	Embryo stage	Inclusion criteria	Exclusion criteria	N c
Kovacs *et al.* (2019)	Hungary	RCT	Oct 2012 to Apr 2015	Fresh: 34	Fresh: 26	IVF/ICSI	D3/Blastocyst	age <36 years 1st/2nd cycle autologous oocyte use normal ovarian reserve eSET	advanced stage endometriosis polycystic ovary syndrome surgical sperm extraction PGD	b l v b g d p v
Insua *et al.* (2017)	Spain	RCT	Oct 2012 to Apr 2014	Fresh: 216	Fresh: 162	ICSI	D3/Blastocyst	Age 20-38 years 1st/2nd cycle BMI 18-25kg/m^2	severe male factor hydrosalpinx acquired or congenital uterine abnormalities endocrinopathies recurrent pregnancy losses endometriosis low-responder patients	E l v b g d p N N
Zaninovic *et al.* (2015)	The USA	Retrospective cohort study	2012 to May 2014	Fresh: 947	Fresh: 714	IVF	D3	Not mentioned	Frozen ET and PGD/S	N
Mascarenhas *et al.* (2018)	The UK	Retrospective cohort study	Jan 2014 to Oct 2015	Fresh: 341 Frozen: 150	Fresh: 252 Frozen: 132	IVF/ICSI	D3/Blastocyst	Not mentioned	Not mentioned	E l v b g d p v d
Bingxin *et al.* (2021)	China	Retrospective cohort study	January 2016 to December 2019	Fresh: 1875	Fresh: 1445	IVF/ICSI	D3/Blastocyst	SI group were selected to match the ages and oocytes of the TLI group	Not mentioned	E l v b g d p v M S M

Figures

Fig. 1

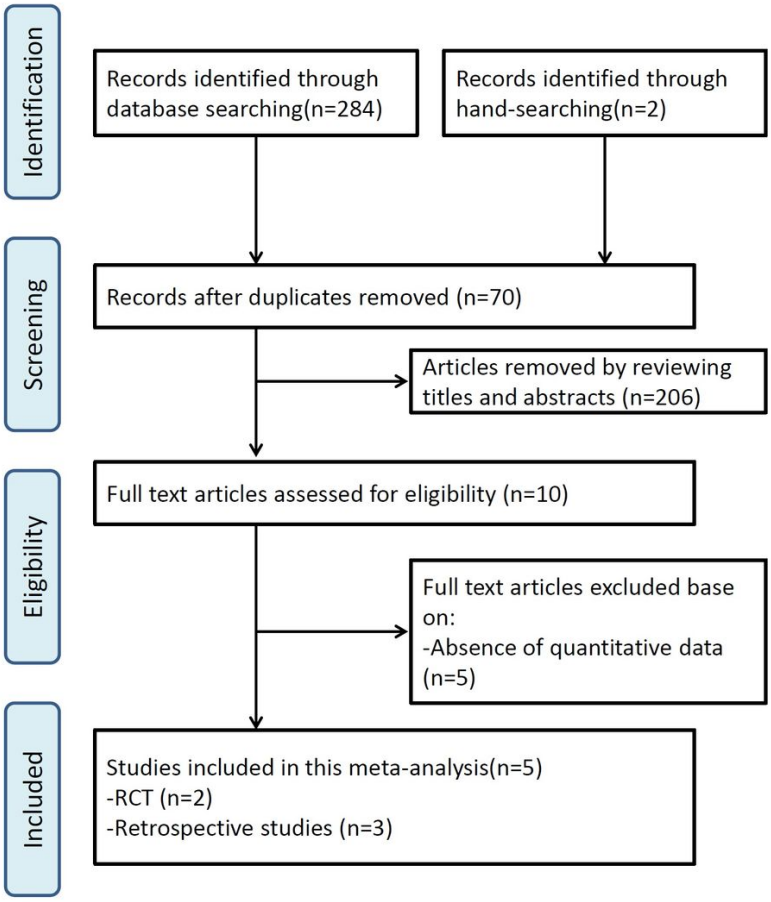

Figure 1

PRISMA flow diagram of study selection.

Fig. 2

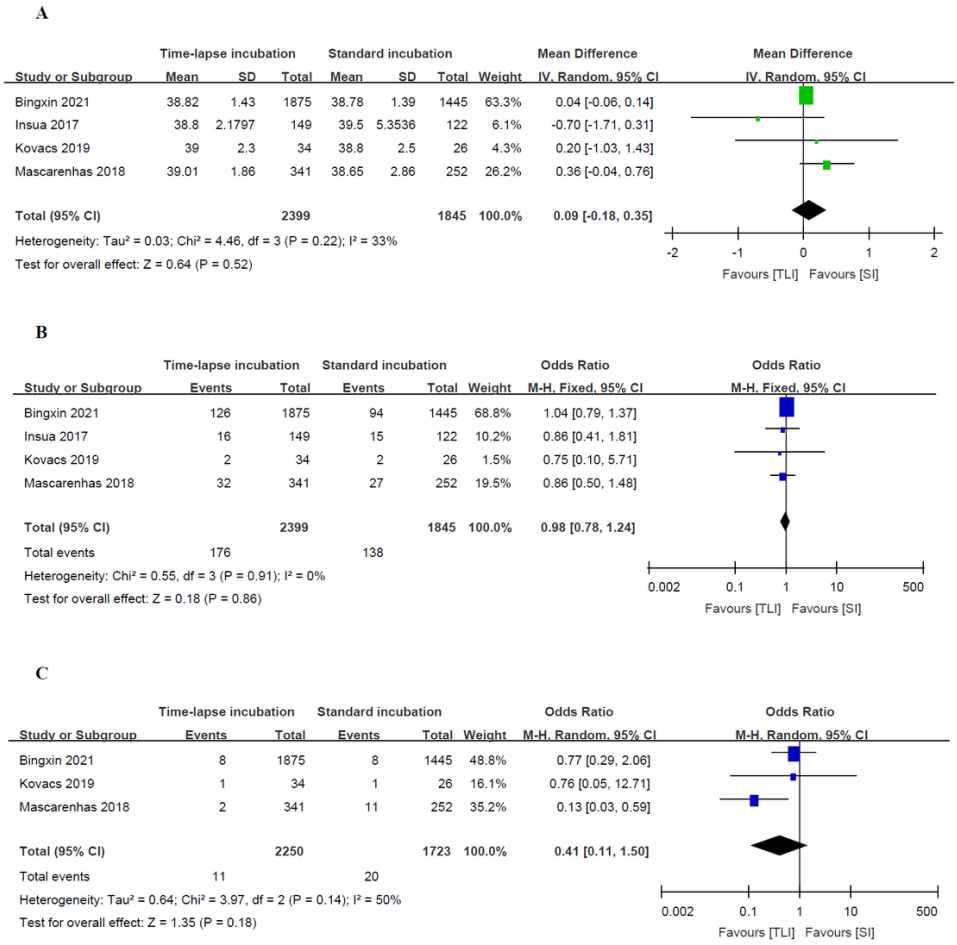

Figure 2

Forest plots comparing gestational weeks at delivery with TLI and SI.

(A) Forest plot of weeks at delivery per randomized singleton pregnancy woman in the studies comparing time-lapse vs. standard incubator. (B) Forest plot of preterm birth per randomized singleton pregnancy woman in the studies comparing time-lapse vs. standard incubator. (C) Forest plot of early preterm birth per randomized singleton pregnancy woman in the studies comparing time-lapse vs. standard incubator.

Fig. 3

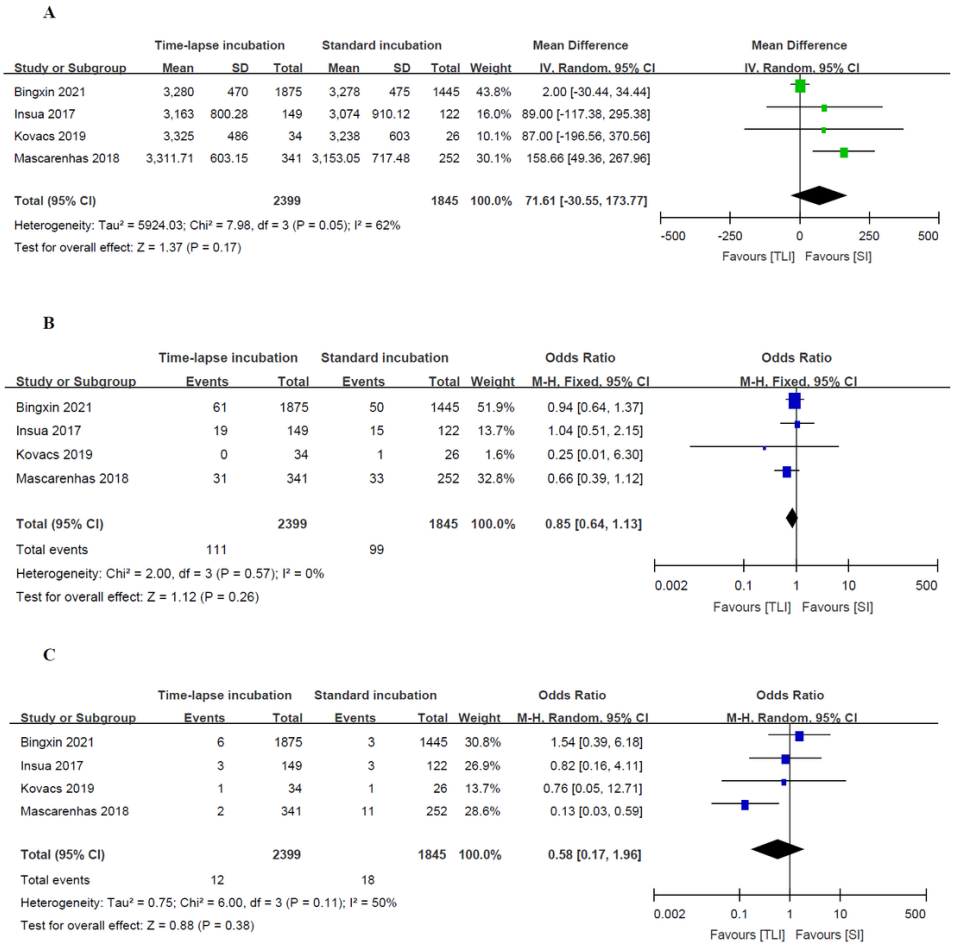

Figure 3

Forest plot of mean birth weight, low birth weight, and very low birth weight comparing TLI vs. SI.

(A) Forest plot of mean birth weight per randomized singleton pregnancy woman in the studies comparing time-lapse vs. standard incubator. (B) Forest plot of low birth weight per randomized singleton live-born infant in the studies comparing time-lapse vs. standard incubator. (C) Forest plot of very low birth weight per randomized singleton live-born infant in the studies comparing time-lapse vs. standard incubator.

Fig. 4

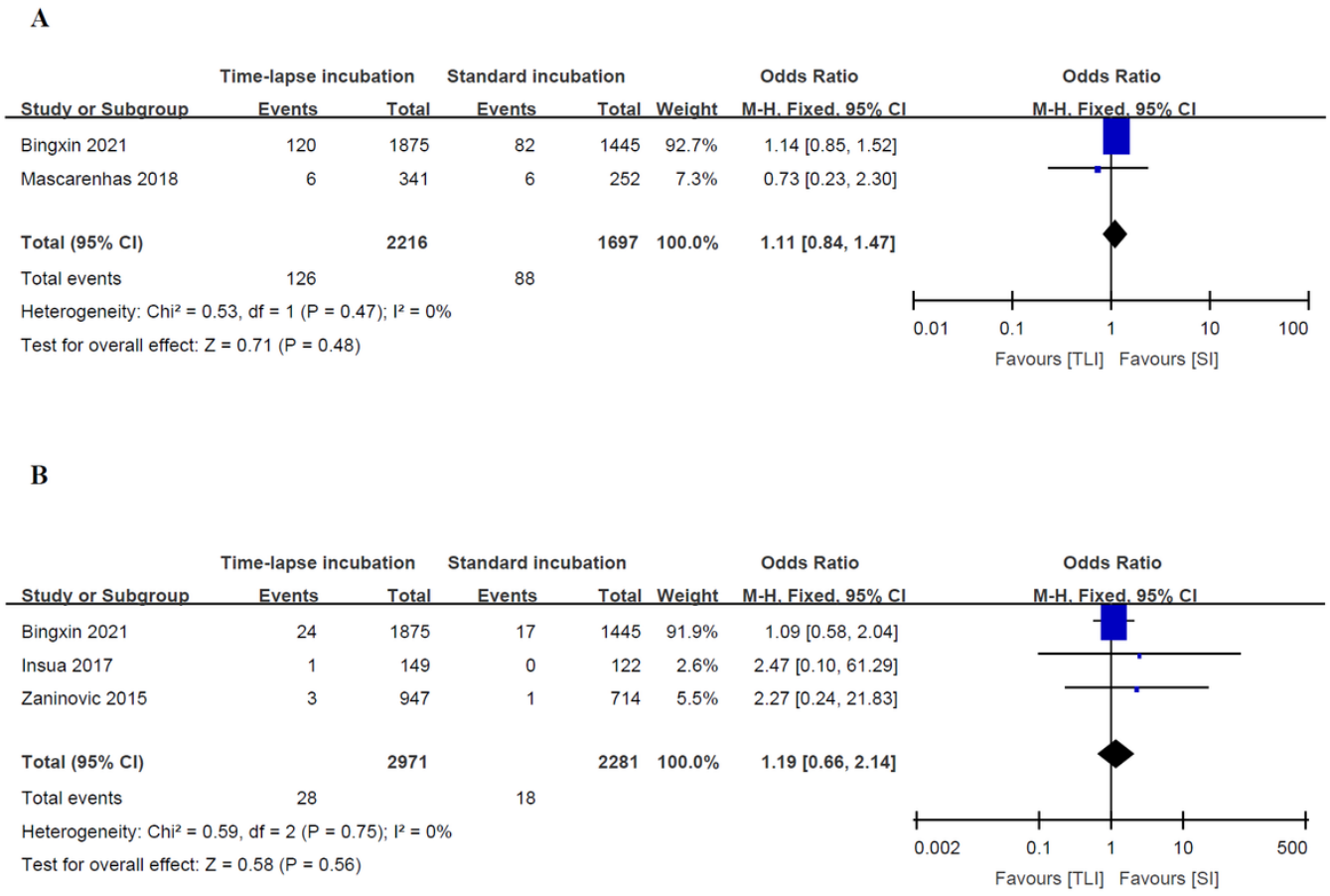

Figure 4

Forest plot of macrosomia and the incidence of malformations in the studies comparing TLI vs. SI.

(A) Forest plot of macrosomia rate per randomized singleton pregnancy woman in the studies comparing time-lapse vs. standard incubator. (B) Forest plot of incidence of congenital malformations per randomized singleton live-born infant in the studies comparing time-lapse vs. standard incubator.

Fig. 5

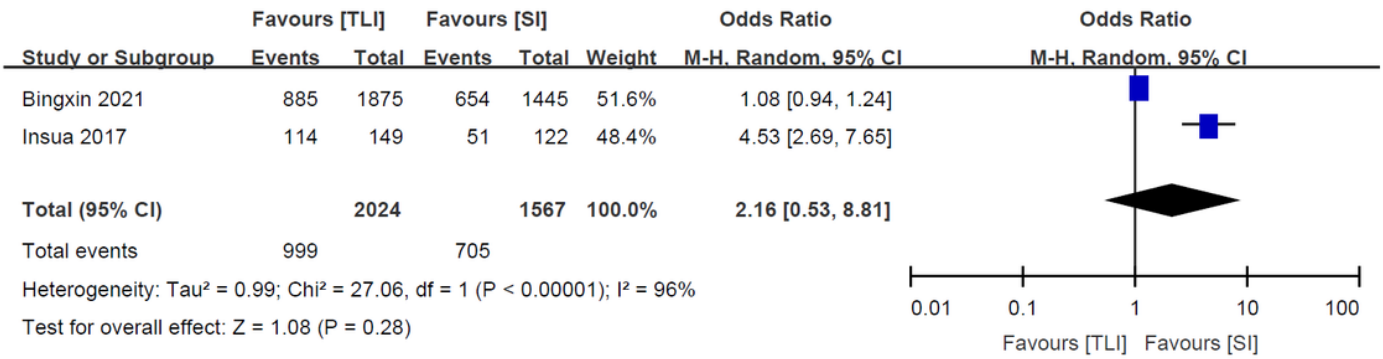

Figure 5

Forest plot of sex ratio in the studies comparing TLI vs. SI.

Fig. 6

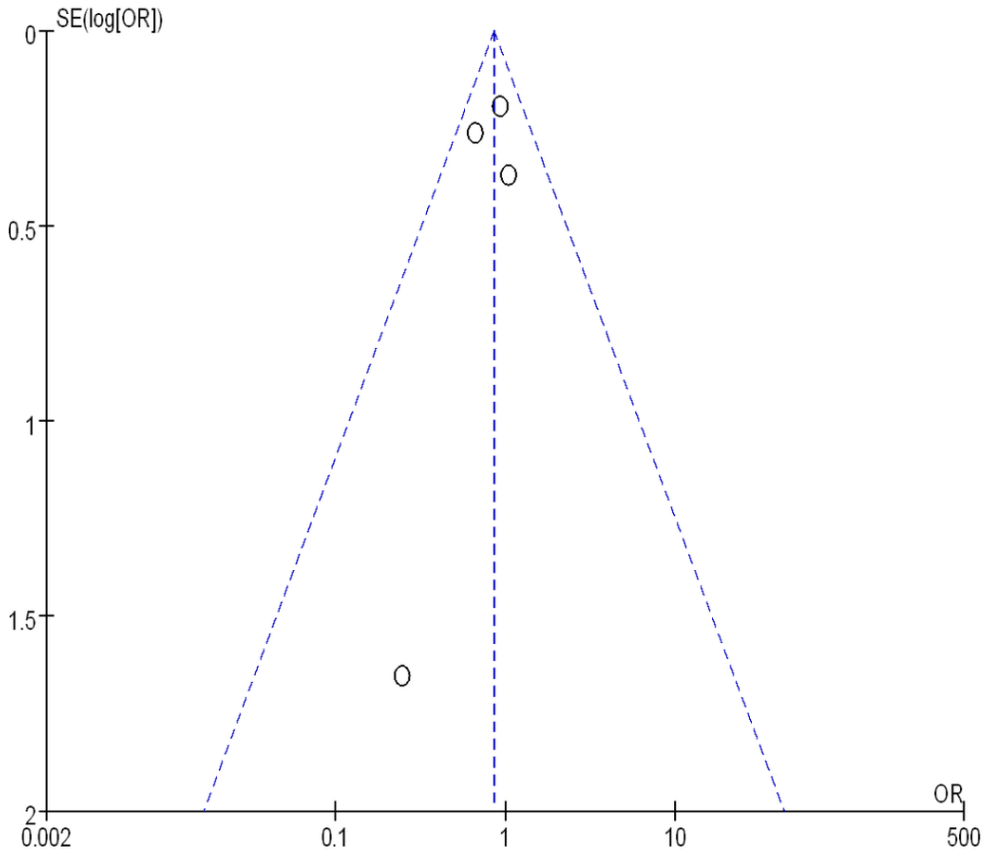

Figure 6

Funnel plots illustrating meta-analysis of live birth weight.

SE=standard error; OR= odds ratios