



# Is modified embryo transfer technique related to an increased pregnancy rate?

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Assisted reproductive technique (ART), especially an application of in vitro fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI+ET) technique, significantly improves the pregnancy outcome in couples with various kinds of infertility, including either male factor, female factor, or combination of both factors,<sup>1-7</sup> and has become a widely accepted method of treatment for infertile couples.<sup>3</sup> However, the IVF/ICSI+ET procedure is an invasive process with very high cost. Many factors, such as woman's age, comorbidity situations, and experiences of physicians, are associated with the success pregnancy rate in every ART cycle. ART consists of several procedures that involve the in vitro handling of both human oocytes and sperm (treatment of a variety of causes of infertility by collecting gametes), or of embryos (creation of embryo from gametes in the laboratory and transferring of the most viable embryo into the uterus), with the objective of setting up a pregnancy.<sup>8</sup> In view of the couples with subfertility, experience of physicians may be one of most controlled factors, because evidence indicates the best methods for every aforementioned step in the ART cycle, which can lead to simplifying and improving the processes with subsequently increased live birth rates from ART, along with a reduction in adverse event.<sup>8</sup> Therefore, many strategies or therapeutic protocols have been modified to look for an innovative and effective procedure during ART in infertility centers or experts.<sup>1,3,4,8</sup> A recent international consensus development study showed the leading problem in top 10 priorities for medical ART is "What are the causes of implantation failure?,"<sup>9</sup> suggesting that any improvement of implantation rate during ET is welcome. However, despite advances in techniques, pregnancy rate is not satisfied with a maximally 35% per ET and implantation after ET seems to be the most critical step in the success of IVF/ICSI-ET treatment.<sup>10</sup> We are happy to learn the following article published in the current issue of the *Journal of the Chinese Medical Association* to address this leading problem—to overcome the rate-limiting step (implantation) in ART.<sup>11</sup>

Gurbuz and Yildiz<sup>11</sup> attempted to determine whether the rotating the ET catheter 360 degrees will increase the implantation rate or clinical pregnancy rate during ET process or not. The result showed that women undergoing the standard procedure or rotating the ET catheter 360 degrees had an implantation rate of 38.0% (509/1338) and 35.5% (324/912) implantation rate, respectively, without statistical significance.<sup>11</sup> Additionally, miscarriage rate, clinical pregnancy rate per ET, or pregnancy rate per ET were all absent of statistically significant difference between both groups,<sup>11</sup> suggesting that this strategy (ET catheter rotation) following ET cannot add any positive impact on the increased pregnancy rate. Although the results of the current study were disappointing, the current study is still worthy of further discussion.

First, the authors' hypothesis was based on the using rotating catheter by 360 degrees while withdrawing it to ensure that the embryo remains in the uterus during the ET process, rather than being removed due to adherence to the cervical mucus in the catheter tip, thereby improving the pregnancy rate, hinting that an increasing contact time between embryo and endometrium may increase the chance of implantation. However, as shown by authors, waiting before catheter withdrawal after ET (supposed to increase the contact time between embryo and endometrium) seemed to be the absence of any positive impact on the increased pregnancy rate.<sup>11</sup> Therefore, it is not surprising to find that the rotation of catheter by 360 degrees did not increase an additional chance for pregnancy rate during the ET procedure, as shown by authors.<sup>11</sup>

Second, the use of the rotation of catheter may support the original hypothesis of the authors as shown above—no association with the removal of cervical mucus attached to the catheter tip in this attempt. As introduced by authors,<sup>11</sup> cleaning the cervix and removing the cervical mucus might result in an increased clinical pregnancy rate and live birth rate. However, a meta-analysis enrolling 8 radical controlled trials including 1715 women showed that the clinical pregnancy rate was similar in women with and without cleaning or removing cervical mucus before the ET procedure (risk ratio [RR] 1.25, 95% confidence interval [CI] 0.96–1.67 in overall; RR 1.12, 95% CI 0.85–1.49 in the cervical mucus removal by the aspiration group; RR 1.73, 95% CI 1.33–2.27 in the cervical mucus removal with a cotton swab; RR 1.06, 95% CI 0.67–1.69 in the cervical mucus removal by the cervical brush group); with resultant conclusion as the possible small benefit of cervical removal before ET.<sup>12</sup> Because the current study did not show any additional benefits on the increased clinical pregnancy in women undergoing rotation of

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catheter during ET,<sup>11</sup> it is in agreement that the rotation of catheter may not be involved in the detachment of cervical mucus which may interfere from implantation after ET.

Third, we are wondering whether the rotation of catheter during ET may stimulate the endometrium or provide a minimal traumatic effect on the endometrium, which are reported to be beneficial on the increased pregnancy rate before ET, although the evidence may be low.<sup>10,13,14</sup> One Cochrane Systematic Review showed there was no evidence of benefits with the following interventions, such as full bladder, removal of cervical mucus, flushing the endocervical canal, or the endometrial cavity.<sup>13</sup> By contrast, a recent multicenter clinical trial showed a minimal traumatic effect (endometrial scratching) may provide a little, but a true difference (95% CI -0.7% to +9.9%) of an increased live birth rate during ET or subsequent ET with RR of 1.24 (95% CI 0.96–1.59), and 95% CI -1.2% to +11.4%, respectively.<sup>10</sup> Additionally, although evidence is uncertain, there is a trend to show the little benefit on the increased live birth/ongoing pregnancy rates if endometrial injection of embryo culture supernatant before ET was performed (odds ratio [OR] 1.11; 95% CI 0.73–1.70).<sup>14</sup> Based on the authors' results, we believe that the rotation of catheter is also not involved in the endometrial injury.

Fourth, by contrast, the authors have mentioned that stimulation of the uterus may decrease the implantation rate after ET. This is based on the concept that uterine contraction may result in the expulsion of intrauterine content. The rotation of catheter by 360 degrees during the ET procedure may stimulate the uterus, with resulting in an increased risk of uterine contraction, which may be harmful on ET. As predicted, the pregnancy rate was really lower in the rotation of catheter group than that in the standard group (35.5% vs. 38%), even though the statistical analysis failed to reach the significant difference.<sup>11</sup> Therefore, we believe that the rotation of catheter in the current study may be associated with overmanipulation of procedure during ET, with resultant unwanted uterine contraction and subsequent failure of implantation of embryo.

Although we may be disappointed by the results of the current study own to the absence of significant improvement of the pregnancy rate after ET because live birth rate remains consistently low, there is no doubt that the better understanding of implantation process will increase our chance to enhance the therapeutic outcome. ART is very expensive, time consuming, and of most importance, psychological and emotional stress bothers these subfertile couples<sup>15–17</sup>; therefore, any innovative treatment to improve the outcome is welcome.

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