Freeze-all versus fresh blastocyst transfer strategy during in vitro fertilisation in women with regular menstrual cycles

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Study question
Is the ongoing pregnancy rate following a freeze-all strategy superior compared with a conventional fresh blastocyst transfer strategy in regular cycling women undergoing in vitro fertilisation (IVF)?

Methods
Randomised controlled trial conducted at eight fertility centres in Denmark, Sweden, and Spain in 460 women (age 18-39 years) with regular menstrual cycles who were starting their first, second, or third treatment cycle of IVF or intracytoplasmic sperm injection. Randomisation was performed on cycle day 2 or 3 to one of two treatments: freeze-all (elective freezing of all embryos)—use of gonadotrophin releasing hormone agonist for ovulation triggering and single frozen-thawed blastocyst transfer in a subsequent natural cycle; or fresh transfer—use of human chorionic gonadotrophin for ovulation triggering and single blastocyst transfer in the fresh cycle. Women in the fresh transfer group with more than 18 follicles larger than 11 mm on the day of triggering had elective freezing of all embryos and postponement of transfer as a safety measure. The primary outcome was ongoing pregnancy rate, defined as a detectable fetal heart beat after eight weeks of gestation, with analysis performed by intention to treat. Secondary outcomes included live birth rate and pregnancy related, obstetric, and neonatal complications.

Study answer and limitations
Ongoing pregnancy rate did not differ significantly between the freeze-all (27.8% (62/223)) and fresh transfer (29.6% (68/230)) groups; risk ratio 0.98, 95% confidence interval (0.87 to 1.10, P=0.76). No significant difference was found in the live birth rate (27.4% (61/223) for freeze-all and 28.7% (66/230) for the fresh transfer group; risk ratio 0.98, 0.87 to 1.10, P=0.83). The risks of pregnancy related, obstetric, and neonatal complications did not differ between the groups except for a higher mean birth weight after frozen blastocyst transfer and an increased risk of prematurity after fresh blastocyst transfer. This study tested the freeze-all strategy in a broad population of women undergoing IVF and so the results might not apply to certain subgroups of women.

What this study adds
In women with regular menstrual cycles, a freeze-all strategy did not result in higher ongoing pregnancy and live birth rates than a fresh transfer strategy.

Funding, competing interests, and data sharing
The study is part of the Reprounion collaborative study, cofinanced by the European Union, Interreg V OKS. See full paper on bmj.com for further details.

Trial registration ClinicalTrials.gov NCT02746562.

Reproductive outcomes for women in freeze-all and fresh transfer groups (intention-to-treat analysis). Data are number/total number (percentage) of women unless stated otherwise

| Primary outcome: ongoing pregnancy | Freeze-all (n=223) | Fresh embryo transfer (n=230) | Difference between groups (percentage points (95% CI)) | Risk ratio (95% CI) | P value |
|-----------------------------------|------------------|-----------------------------|-----------------------------------------------|-------------------|---------|
| Ongoing pregnancy rate/No of randomised women | 62/223 (27.8) | 68/230 (29.6) | −1.8 (−10.5 to 7.0) | 0.98 (0.87 to 1.10) | 0.76 |
| Ongoing pregnancy rate/No of women who started stimulation | 62/223 (27.8) | 68/230 (29.6) | −1.8 (−10.5 to 7.0) | 0.98 (0.87 to 1.10) | 0.76 |
| Ongoing pregnancy rate/No of oocyte retrievals | 62/221 (28.1) | 68/227 (30.0) | −1.9 (−10.8 to 6.9) | 0.97 (0.86 to 1.10) | 0.73 |
| Ongoing pregnancy rate/No of embryo transfers | 57/162 (35.2) | 68/181 (37.6) | −2.4 (−13.2 to 8.4) | 0.96 (0.82 to 1.13) | 0.73 |

Not including women who withdrew their consent. All analyses by intention to treat.
Lockdown-type measures look effective against covid-19

**ORIGINAL RESEARCH** Natural experiment in 149 countries

**Physical distancing interventions and incidence of covid-19**

Islam N, Sharp SJ, Chowell G, et al

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Study question What is the association between policy interventions for physical distancing and the incidence of coronavirus disease 2019 (covid-19)?

Methods Using a natural experiment approach, this study examined the effectiveness of physical distancing interventions on the incidence of covid-19 in 149 countries or regions. Data on daily reported cases of covid-19 were obtained from the European Centre for Disease Prevention and Control, and data on the physical distancing policies were obtained from the Oxford covid-19 Government Response Tracker. Physical distancing interventions examined were school closures, workplace closures, restrictions on mass gatherings, public transport closure, and restrictions on in-country movements (lockdowns). Countries and regions were included if they implemented one of the five physical distancing interventions between 1 January and 30 May 2020. An interrupted time series analysis was used to estimate trends in incidence rate ratios (IRR) of covid-19 before and after the interventions. IRRs were synthesised across countries using random effects meta-analysis.

Study answer and limitations Data from 149 countries showed that physical distancing interventions were associated with an average a 13% reduction (IRR 0.87, 95% confidence interval 0.85 to 0.89) in the incidence of covid-19. Closure of public transport was not associated with any additional reduction in incidence when the other four physical distancing interventions were in place (pooled IRR with and without public transport closure was 0.85, 95% confidence interval 0.82 to 0.88; n=72 countries, and 0.87, 0.84 to 0.91; n=32, respectively). Earlier lockdowns were associated with a larger reduction in the incidence of covid-19 (pooled IRR 0.86, 0.84 to 0.89; n=105) compared with delayed implementation after other physical distancing interventions were in place (pooled IRR 0.90, 0.87 to 0.94; n=41). Major limitations of this study include possible under-reporting of covid-19 cases and the inability to determine the associations between the extent and intensity of these interventions and the incidence of covid-19.

**COMMENTARY** But evidence is undermined by unreliable data on incidence

In their study, Islam and colleagues provide important preliminary evidence for the effectiveness of physical distancing (referred to by some as social distancing) measures in controlling the covid-19 pandemic, including closures of schools and workplaces, restrictions on mass gatherings and public events, and restrictions on movement (lockdowns). This supporting evidence is desperately needed as these measures are challenged around the world.

The greatest strength of this study is its reliance not on hypothetical modelling but on actual data. Although the use of some modelling techniques remained necessary, primary data reflected actual test results. Unfortunately, using such results is also the study’s greatest weakness. Specifically, the authors relied on “daily reported cases” compiled from 149 independent countries; data subject to variable quality, accuracy, and inconsistent testing practices.

As a result, caution is warranted when interpreting the findings. These flaws are not the fault of the authors, who have done admirable work with the information available. But the collection and reporting of test data by regional and national authorities does not reflect the same commitment to scientific rigour. In particular, a lack of coordination and standardisation in both testing and reporting has undermined the reliability of the authors’ conclusions, despite high quality analyses.

For example, the failure to implement a coordinated, consistent testing strategy in the US means that changes in numbers of cases might simply reflect changes in testing practices rather than the effects of an intervention.

This is true not only for “total diagnosed cases” but also for incidence rates. Early shortages of testing kits in the US led to testing restricted to only people with symptoms or those with known exposure to covid-19. Once testing expanded beyond these groups (that we had reason to believe would test positive), we would naturally expect the ratio of positive test results to tests administered to fall. Because of poor coordination, supervision, and consistency of testing strategies across the US, it is impossible to know how we might accurately account for variable testing practices in any analysis of covid-19 incidence.

**Political responsibility** Important aspects of the design and conduct of testing strategies are often out of the control of public health agencies. In the US, local public health agencies are notoriously underfunded, understaffed, and dependent on the availability of tests and other resources. The role of these agencies is not to assemble high quality data for study but to respond to changing public health needs with whatever resources are available. It is the responsibility of politicians and policy makers to harmonise testing and reporting strategies for covid-19—at a national or, ideally, international level—so that data on incidence are meaningful, comparable, and useful for evaluating the effectiveness of pandemic responses. Whatever the reason for variation in testing practices, the result is that data accrued so far are inadequate for use in scientific evaluations of physical distancing measures.
What this study adds Physical distancing interventions were associated with reductions in the incidence of covid-19. Public transport closure showed little effect when the other four physical distancing interventions were in place. In combination with school and workplace closures, restrictions on mass gatherings seemed to be a key component of an effective physical distancing strategy. Earlier implementation of lockdown was associated with a larger reduction in the incidence of covid-19. These findings might support policy decisions as countries prepare to impose or lift physical distancing measures in current or future epidemic waves.

void

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0.85\(\pm\)0.82 to 0.88
0.87\(\pm\)0.84 to 0.91
0.85\(\pm\)0.81 to 0.89
0.91\(\pm\)0.84 to 0.98
0.91\(\pm\)0.82 to 1.00
0.93\(\pm\)0.71 to 1.23

Association between the combinations of physical distancing interventions and change in incidence of coronavirus disease 2019. \(I^2\) = an estimate of the percentage of total variation across the countries that is due to heterogeneity rather than chance.

The study by Islam and colleagues provides support for physical distancing but cannot be definitive for the reasons outlined. The fact that effectiveness is discernible across so many different data collection strategies and individual countries is, however, strongly suggestive of the effectiveness of these measures.

Control strategies informed by flawed data might advance public health aims in the short term but do lasting damage to our ability to effect behavioural change through evidence in the future. We must be careful, then, not to mislead or overplay politically convenient findings and risk violating the public trust necessary for an effective pandemic response.

This study is as good as it could be given the data available, but it would have been so much more valuable had “daily reported cases” been underpinned by meaningful data on testing. Calls for a coordinated, global public health infrastructure for a pandemic response have been growing for decades. Only by acknowledging our failures in systematic testing and data collection can we learn from our mistakes and avoid repeating them.

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Diagnostically accuracy of serological tests for covid-19

Bastos ML, Tavaziva G, Abidi SK, et al

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What is the diagnostic accuracy of serological tests for coronavirus disease 2019 (covid-19)?

Methods
Eligible studies in this systematic review and meta-analysis measured the sensitivity or specificity, or both, of a serology test for covid-19 compared with a reference standard of viral culture or reverse transcriptase polymerase chain reaction. Peer reviewed studies and preprints of studies published or posted between 1 January and 30 April 2020 were considered. The main outcome, estimated using meta-analysis, was pooled sensitivity and specificity, stratified by serology test method (enzyme linked immunosorbent assays (ELISAs), lateral flow immunoassays (LFIs), or chemiluminescent immunoassays (CLIs)) and immunoglobulin class (IgG or IgM, or both).

Study question
What is the diagnostic accuracy of serological tests for covid-19?

Methods
Find this at: http://dx.doi.org/10.1136/bmj.m2516

Summary of main findings

| Test method | Classification by serology test | Results per 1000 patients tested (95% CI) |
|-------------|---------------------------------|-------------------------------------------|
|             |                                 | 5% prevalence | 10% prevalence | 20% prevalence |
| Population: SARS-CoV-2 infected | | | | |
| ELISA (IgG or IgM): | | | | |
| 9 studies, 766 samples. | Correctly classified as infected | 42 (38 to 45) | 84 (76 to 91) | 169 (151 to 182) |
| Pooled sensitivity 84.3% (95% CI 75.6% to 90.9%). | Incorrectly classified as uninfected | 8 (5 to 12) | 16 (9 to 24) | 31 (18 to 49) |
| LFIA (IgG or IgM): | | | | |
| 11 studies, 2660 samples. | Correctly classified as infected | 32 (25 to 40) | 66 (49 to 79) | 132 (99 to 159) |
| Pooled sensitivity 66.0% (95% CI 49.3% to 79.3%). | Incorrectly classified as uninfected | 17 (10 to 25) | 34 (21 to 51) | 68 (41 to 101) |
| CLIA (IgG or IgM): | | | | |
| 2 studies, 375 samples. | Correctly classified as infected | 49 (23 to 50) | 98 (46 to 100) | 196 (92 to 200) |
| Pooled sensitivity 97.8% (95% CI 46.2% to 100%). | Incorrectly classified as uninfected | 1 (0 to 27) | 2 (0 to 54) | 4 (0 to 108) |
| Population: not infected with SARS-CoV-2 | | | | |
| ELISA (IgG or IgM): | | | | |
| 6 studies, 1109 samples. | Correctly classified as uninfected | 931 (884 to 974) | 182 (837 to 912) | 784 (744 to 809) |
| Pooled specificity 97.6% (95% CI 93.2% to 99.4%). | Incorrectly classified as infected | 19 (9 to 59) | 18 (9 to 64) | 16 (8 to 56) |
| LFIA (IgG or IgM): | | | | |
| 11 studies, 2874 samples. | Correctly classified as uninfected | 918 (896 to 933) | 169 (849 to 884) | 773 (754 to 786) |
| Pooled specificity 96.6% (95% CI 94.3% to 98.2%). | Incorrectly classified as infected | 32 (17 to 54) | 31 (16 to 51) | 27 (14 to 46) |
| CLIA (IgG): | | | | |
| 9 studies, 2804 samples. | Correctly classified as uninfected | 929 (598 to 949) | 880 (566 to 899) | 782 (503 to 799) |
| Pooled specificity 97.8% (95% CI 62.9% to 99.9%). | Incorrectly classified as infected | 21 (1 to 352) | 20 (1 to 334) | 18 (1 to 297) |

What this study adds
In the existing evidence base, reported estimates of sensitivity and specificity of serology tests for covid-19 are unreliable and have limited generalisability to outpatient settings and to point-of-care testing. Caution is warranted if using the tests for clinical decision making. Evidence does not support the use of existing point-of-care serology tests for covid-19.

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