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**ORIGINAL RESEARCH** Systematic review and meta-analysis

**Progression to type 2 diabetes in women with a known history of gestational diabetes**

Vounzoulaki E, Khatun K, Abner SC, Tan BK, Davies MJ, Gillies CL

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**Study question** What is the risk of developing type 2 diabetes in women who have had gestational diabetes compared with those who have not?

**Methods** An extensive search of Medline and Embase between January 2000 and December 2019 was carried out. Studies in English were identified that looked at the subsequent development of type 2 diabetes in women who had gestational diabetes and those who did not.

**Study answer and limitations** 20 studies were found assessing 1 332 373 women (67 956 with gestational diabetes and 1 264 417 without). The overall relative risk for type 2 diabetes mellitus in studies with follow-up for one to 25 years, was almost 10 times higher in women with previous gestational diabetes mellitus than in healthy controls (9.51, 95% confidence interval 7.14 to 12.67, P<0.001). In populations of women with previous gestational diabetes, the cumulative incidence of type 2 diabetes mellitus was 16.46% (95% confidence interval 16.16% to 16.77%) over 11.4 years in women of mixed ethnicity, 15.58% (13.30% to 17.86%) over 6.0 years in a predominantly non-white population, and 9.91% (9.39% to 10.42%) over 7.3 years in a white population. Limitations were that only studies published in English were included; broad ethnic categories were used, owing to a lack of data; and it was not possible to identify the main sources of heterogeneity in the effect estimates.

**What this study adds** Results confirm that women who had gestational diabetes have an increased risk of developing type 2 diabetes compared with those who did not and suggests that the risk might be higher now than was previously thought. The relative risk was higher in studies with follow-up between one and five years (relative risk 17.1) than in studies with follow-up of more than 10 years (relative risk 8.1).

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**Systematic review registration** CRD42019123079.
Viral persistence during recovery from covid-19

ORIGINAL RESEARCH Retrospective cohort study

Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020


Methods This was a retrospective cohort study of 96 patients with laboratory confirmed coronavirus disease 2019 (covid-19) consecutively admitted to the First Affiliated Hospital, Zhejiang University, from 19 January 2020 to 15 February 2020. Data were collected to 20 March 2020. 3497 respiratory, stool, serum, and urine samples were collected from the patients after admission and evaluated for SARS-CoV-2 ribonucleic acid (RNA) viral load by plotting cycle threshold values, a measure of nucleic acid concentration, on to the standard curve constructed based on the standard product. Epidemiological, clinical, and laboratory characteristics and treatment and outcomes data were obtained from electronic medical records, and the relation between clinical data and disease severity was analysed.

Study question What are the viral loads at different stages of disease progression in patients infected with the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)?

Study answer and limitations All patients were confirmed as having SARS-CoV-2 infection by testing sputum and saliva samples. RNA was detected in the stool of 55 (59%) patients and in the serum of 39 (41%) patients. The urine sample from one patient was positive for SARS-CoV-2. From symptom onset, the median duration of virus in stool (22 days, interquartile range 17-31 days) was significantly longer than in serum.

Important limitation PCR is unable to differentiate between actual viral replication and non-viable, and therefore non-infectious, viral material.

PCR results in stool were often discordant with those in serum or respiratory samples, and thus it is unclear whether these differences reflect different clinical courses or differences in PCR test characteristics.

Isolation has long been regarded as the most effective safeguard against the spread of infectious diseases, and during the current covid-19 pandemic many thousands of potentially infected patients have been isolated globally. Different opinions exist about the duration of isolation, not least because data on the persistence and infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in various body fluids have been scarce.

In this issue, Zheng and colleagues describe viral load dynamics in 96 patients with SARS-CoV-2. Viral loads in respiratory samples, stool, serum, and urine were tested using polymerase chain reaction (PCR) techniques during four weeks of hospital admission. At the end of these four weeks more than half of the patients still tested positive for SARS-CoV-2 in stool samples and over a third of patients in serum samples, with worrying implications for disease control.

By contrast, all samples in a small European case series, including those from nasopharyngeal swabs and stools, became SARS-CoV-2 negative within two weeks for all surviving patients. It is not clear whether these differences reflect different clinical courses or differences in PCR test characteristics.

PCR was first used more than 30 years ago. Since then technical improvements have made PCR the tool of choice for specific enzymatic amplification of nucleic acid in vitro. An important limitation of PCR testing, however, is the inability to differentiate between actual viral replication and the detection of non-viable, and therefore non-infectious, viral material.

This has been a key challenge in previous epidemics when assessing the infectiveness of recovering patients and determining the clinical relevance of detecting viral RNA in stools is particularly difficult. In Ebola virus disease, viral RNA has been found in stool samples after clearance of viraemia in blood in recovering patients, yet attempts to recover virus from cell cultures have so far failed. Similarly, in patients with Middle East respiratory syndrome (MERS) coronavirus infection, RNA was usually detected from faeces, but viral isolation trials had negative outcomes.

During the 2002-03 SARS-CoV-1 pandemic, positive PCR results in stool were also reported. These data, combined with observations of indirect transmission through contaminated surfaces and fomites, led to the suggestion of faecal-oral transmission of SARS-CoV-1.

What can we conclude from the linked study? Should patients be kept in isolation as long as they show signs of viral RNA shedding? In terms

Commentary Isolating patients for a month or more may not be feasible

PCR is unable to differentiate between actual viral replication and non-viable, and therefore non-infectious, viral material.

Roos E Barth
r.e.barth@umcutrecht.nl

Maneke J A De Regt
See bmj.com for author details
of containment of the disease this could be advocated. However, the impact on healthcare systems, virology laboratories, and, most importantly, patients kept in isolation for at least a month, would be enormous. However, meticulous hand and toilet hygiene could be warranted and should reduce considerably the clinical relevance of viral shedding from stool.

It remains necessary to accept some uncertainties in these challenging times and to rely on clinical improvement from covid-19 to inform strategies for ending isolation. Such uncertainty is reflected in proposals from institutions such as the US Centers for Disease Control and Prevention, the National Health Service, and European Centre for Disease Prevention and Control, all of which advocate combinations of testing and other public health measures to reduce the risk of transmission. More epidemiological data, testing, and mathematical modelling will be needed to fully understand the clinical relevance of viral shedding from various body fluids in patients recovering from covid-19. Meanwhile, policy makers, healthcare workers, and patients should continue to cooperate to make the best use of available scientific and clinical knowledge to limit the spread of the virus, without putting too much strain on healthcare systems that are already stretched to their limits.

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What this study adds SARS-CoV-2 can be detected for longer in stool samples than in respiratory and serum samples. The virus persists longer and with higher load and peaks later in the respiratory tissue of patients with severe disease. Further work might investigate to what extent these present an infection risk.

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Graduated compression stockings as adjuvant to pharmaco-thromboprophylaxis in elective surgical patients (GAPS study)

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Study question Does the use of graduated compression stockings offer any adjuvant benefit when pharmaco-thromboprophylaxis is used for venous thromboembolism prophylaxis in patients undergoing elective surgery?

Methods This randomised, non-inferiority clinical trial enrolled participants from seven hospitals across the United Kingdom. 1905 inpatients aged 18 years or older who were undergoing elective surgery (most commonly, general—higher or lower gastrointestinal and obstetrics and gynaecology) and were assessed to be at moderate or high risk of venous thromboembolism were eligible and consented to participate. Participants were randomly assigned (1:1) to receive either low molecular weight heparin (LMWH) pharmaco-thromboprophylaxis alone or LMWH pharmaco-thromboprophylaxis and graduated compression stockings. The primary outcome was imaging confirmed lower limb deep vein thrombosis with or without symptoms, or pulmonary embolism with symptoms up to 90 days after surgery.

Study answer and limitations Of 1905 eligible participants, 1858 were included in the intention to treat analysis (17 were identified as ineligible after randomisation and 30 did not undergo surgery). A primary outcome event occurred in 16 of 937 (1.7%) participants in the LMWH alone group compared with 13 of 921 (1.4%) in the LMWH and graduated compression stockings group. The risk difference between the two groups was 0.30% (95% confidence interval −0.65% to 1.26%). This result effectively excludes a difference of more than 1.26%, which is less than the predefined non-inferiority margin of 3.5%. 281 of 1858 (15.1%) participants did not receive a duplex ultrasound scan, which could have detected additional patients with deep vein thrombosis without symptoms.

What this study adds This study has shown that administration of pharmaco-thromboprophylaxis alone is non-inferior to a combination of pharmaco-thromboprophylaxis and graduated compression stockings in patients undergoing elective surgery and assessed to be at moderate or high risk of venous thromboembolism.

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Trial registration ISRCTN13911492.