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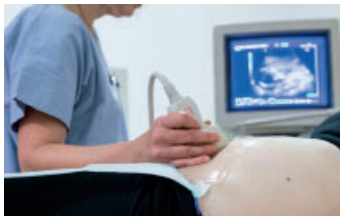

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ORIGINAL RESEARCH Population based cohort study

Association of first trimester prescription opioid use with congenital malformations

Bateman BT, Hernandez-Diaz S, Straub L, et al

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Study question Is exposure to prescription opioids in the first trimester associated with major congenital malformations?

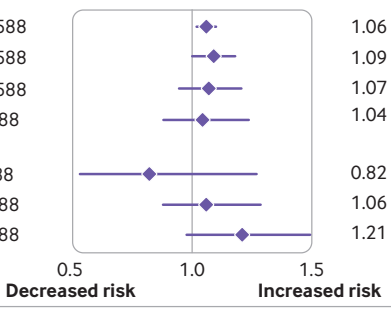
Methods A study was conducted using cohorts of pregnant women linked to their liveborn infants nested in the US Medicaid Analytic eXtract (MAX 2000-14) and the MarketScan Research Database (MarketScan, 2003-15). Exposure was defined as two or more dispensations of any opioid during the first trimester. Validated algorithms were used to define malformations previously associated with opioid exposure (see figure). Relative risks and 95% confidence intervals were estimated using propensity score stratification to adjust for potential confounders and proxies for confounders. Estimates from each database were combined using meta-analysis.

Study answer and limitations In this cohort study including 1 602 580 publicly insured (MAX) and 1 177 676 commercially insured (MarketScan) pregnant women, pooled unadjusted relative risk estimates were raised for all outcomes but shifted substantially toward the null after adjustment; for malformations overall (relative risk 1.06, 95% confidence interval 1.02 to 1.10), cardiovascular malformations overall (1.09, 1.00 to 1.18), ventricular septal defect (1.07, 0.95 to 1.21), atrial septal defect/patent foramen ovale (1.04, 0.88 to 1.24), neural tube defect (0.82, 0.53 to 1.27), and clubfoot (1.06, 0.88 to 1.28). The relative risk for oral clefts remained raised after adjustment (1.21, 0.98 to 1.50), with a higher risk of cleft palate (1.62, 1.23 to 2.14). Limitations of the study include the potential for residual confounding and possible selection bias.

What this study adds The findings suggest that prescription opioids used during the first trimester are not major teratogens, although clinicians and patients should be aware of a potential small increase in risk of oral clefts linked with use.

Funding, competing interests, and data sharing This study was supported by grant R01-DA044293 from the National Institute on Drug Abuse. No competing interests. No additional data available.

Cohort	No of events/total: Opioids	No of events/total: Unexposed	Relative risk (95% CI)	Relative risk (95% CI)
Any congenital malformation	3393/82 504	91 892/2 684 588		1.06 (1.02 to 1.10)
Any cardiovascular malformation	904/82 504	23 198/2 684 588		1.09 (1.00 to 1.18)
Ventricular septal defect	417/82 504	11 683/2 684 588		1.07 (0.95 to 1.21)
Secundum atrial septal defect/ patent foramen ovale	215/82 504	5542/2 684 588		1.04 (0.88 to 1.24)
Neural tube defect	34/82 504	973/2 684 588		0.82 (0.53 to 1.27)
Clubfoot	174/82 504	4119/2 684 588		1.06 (0.88 to 1.28)
Oral cleft	137/82 504	3122/2 684 588		1.21 (0.98 to 1.50)



Risk of congenital malformations (primary outcomes) in infants after exposure to opioids during the first trimester: main analyses (pooled estimates and propensity score stratified)

Covid-19 controversies: the tocilizumab chapter

ORIGINAL RESEARCH Randomised controlled trial

FAST TRACK

Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019

Veiga VC, Prats JAGG, Farias DLC, et al; for the Coalition covid-19 Brazil VI

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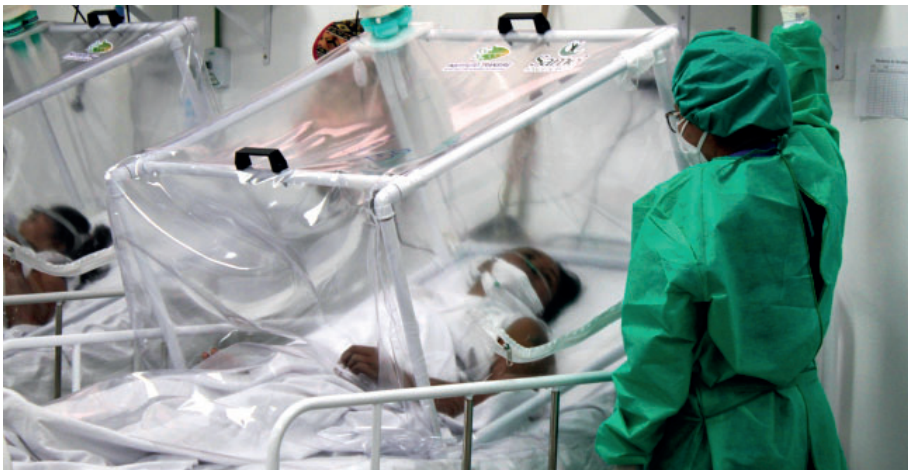

Study question Does the interleukin 6 inhibitor tocilizumab improve clinical outcomes for patients with severe or critical coronavirus disease 2019 (covid-19)?

Methods This randomised, open label, superiority trial was conducted in nine hospitals across Brazil. Eligible participants were adults (≥18 years) with confirmed covid-19 who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, or ferritin).

The data monitoring committee recommended stopping the trial early, after 129 patients had been enrolled, because of an increased number of deaths at 15 days in the tocilizumab group. Patients were randomised 1:1 to receive tocilizumab (single intravenous infusion of 8 mg/kg) plus standard care (n=65) versus standard care alone (n=64). The primary outcome was clinical status at 15 days using a seven level ordinal scale.

Study answer and limitations All patients in the tocilizumab group and two in the standard care group received tocilizumab. 18 of 65 (28%) patients in the tocilizumab group and 13 of 64 (20%) in the standard care group died or were receiving mechanical ventilation at day 15 (odds ratio 1.54, 95% confidence interval 0.66 to 3.66; P=0.32). Death at 15 days occurred in 11 (17%) patients in the tocilizumab group compared with two (3%) in the standard care group (odds ratio 6.42, 95% confidence interval

COMMENTARY The signals from other trials are broadly positive but not definitive

With hospitals and intensive care units at or exceeding capacity in much of the world, discovering life-saving treatments for covid-19 is second only to global vaccination efforts to stop the horrific impact of this disease.

Tocilizumab, a humanised monoclonal antibody that inhibits interleukin 6 mediated signalling by blocking interleukin 6 from binding to receptors, was an early front runner in the race to find treatments for severely ill patients.[2-5] However, conflicting results from several randomised clinical trials, along with corticosteroids becoming standard care for patients admitted to hospital who required oxygen, tempered enthusiasm for its use.[6-9] Now, Veiga and colleagues report a randomised trial from Brazil that compared tocilizumab with standard care in 129 patients with covid-19.[10] Surprisingly, the trial was stopped early because tocilizumab was associated with increased deaths at day 15. Should tocilizumab be abandoned? The answer is not straightforward.

The results of the RECOVERY trial are eagerly awaited to further inform tocilizumab's role

In recent weeks, preprinted results from 803 critically ill participants in the REMAP-CAP trial found tocilizumab decreased in-hospital mortality compared with standard care (28% *v* 35.8%, adjusted odds ratio for survival 1.64, 95% confidence interval 1.14 to 2.35) and reduced progression to intubation, extracorporeal membrane oxygenation, or death.[11] In the REMAP-CAP population, tocilizumab appeared to be life saving.

Discrepant results

Possible explanations for these discrepant results might lie in differences in coadministered treatments, populations, or timing. Both REMAP-CAP and the trial by Veiga and colleagues administered corticosteroids to more than 80% of participants. This is highly relevant given the reported mortality benefit of corticosteroids for patients requiring oxygen, and the potential concern of additive immunosuppression.[12] Remdesivir was not used in the trial from Brazil and was used infrequently in REMAP-CAP. Thus, neither steroids nor remdesivir likely explain the difference.

Differences existed in the trial populations, as well as in the timing of treatment with tocilizumab. Whereas REMAP-CAP enrolled critically ill patients within 24 hours of their requirement for high flow oxygen by nasal canula, non-invasive ventilation, or mechanical ventilation, Veiga and colleagues enrolled predominantly moderately ill patients. The deaths in the Brazilian trial, however, were largely among patients who received tocilizumab within 24 hours of mechanical ventilation, suggesting this is not the explanation.

In a third trial (COVACTA, also in preprint), a post hoc subgroup analysis of patients requiring high flow oxygen by nasal canula found that tocilizumab significantly improved clinical status at day

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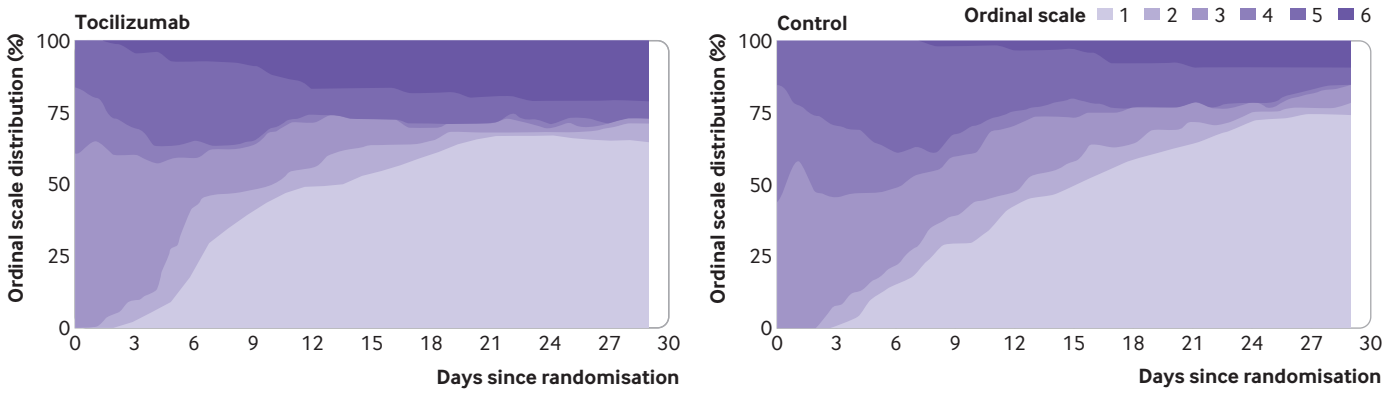

Relative distribution of patient status over time stratified by treatment group. Six level ordinal scale—1: not admitted to hospital; 2: admitted to hospital, not receiving supplemental oxygen; 3: admitted to hospital, receiving supplemental oxygen; 4: admitted to hospital, receiving non-invasive ventilation or high flow oxygen through a nasal cannula; 5: receiving mechanical ventilation; 6: death

1.59 to 43.2). This was an open label trial; the sample size was relatively small; the distribution of the seven level ordinal scale at 15 days was not compatible with proportional odds assumptions, which required the outcome being reclassified as a binary variable; and after randomisation, information was collected on concomitant treatment into broad classes: antivirals, corticosteroids, and antibiotics. These co-interventions were administered similarly for patients assigned to both treatment groups up to day 15. It was not possible to report use of these drugs according to specific agents.

What this study adds Among patients with severe or critical covid-19, tocilizumab plus standard care was not superior to standard care alone in improving clinical status at 15 days and might increase mortality.

Funding, competing interests, and data sharing
Coalition covid-19 Brazil funded the trial. The exploratory laboratory analysis was conducted and funded by Fleury Laboratory (São Paulo, Brazil). Instituto Votorantim provided a donation for the purchase of tocilizumab for this study. See full paper on bmj.com for competing interests. Coalition covid-19 Brazil executive committee will oversee data sharing.
Study registration ClinicalTrials.gov NCT04403685.

14.[8] In analyses of the whole trial population, patients given tocilizumab were discharged from hospital earlier (20 *v* 28 days) and had lower risk of progression to clinical failure than placebo controls, but 28 day mortality did not differ. Finally, the EMPACTA placebo controlled trial found that tocilizumab reduced risk of progression to mechanical ventilation or death among patients predominantly receiving low flow oxygen, but did not improve 28 day survival.[13]

Taken together, the randomised evidence published before the REMAP-CAP preprint suggests significantly less clinical deterioration among patients treated with tocilizumab but no mortality benefit across heterogeneous populations.[14]

Immune activation

These trials might have differed in participants' patterns of immune activation. Veiga and colleagues explicitly enriched their trial population by requiring elevated levels of at least two non-specific inflammatory markers. Most participants in REMAP-CAP also met these inflammatory criteria for both C reactive protein and ferritin. It is, however, unclear whether these non-specific markers are a reasonable sample enrichment strategy for trials of anti-interleukin 6 treatment. Patients admitted to hospital with covid-19 have substantial immune heterogeneity that is not captured by non-specific markers.[15]

Both innate and adaptive immune activation seem to have critical roles, and although a relation might exist between plasma interleukin 6 and dysregulated T cell activation, this correlation is far from proven.[16] Even assuming that plasma interleukin 6 is correlated with hyperactive T cell activation, a causal relation is yet to be shown or even inferred between interleukin 6 and unfavourable outcomes. Treatments for covid-19 are complex, and controversies remain around selecting the "right" patients, even for treatments now considered standard care.

The signal for harm in the trial by Veiga and colleagues, although alarming, is based on relatively few deaths. The data safety board appropriately prioritised patient safety and recommended stopping the trial early; however, the high death rate in mechanically ventilated patients given tocilizumab and lack of deaths in controls requiring high flow oxygen or non-invasive ventilation could be due to chance. Effects might be overestimated when trials are stopped early and small datasets present fragile results.[17]

The totality of randomised data evaluating tocilizumab neither overwhelmingly support nor convincingly refute routine use. The harm reported by Veiga and colleagues is an outlier in a small trial. On balance of evidence, tocilizumab is unlikely to be life threatening. The mortality benefit reported by REMAP-CAP is also a statistical outlier, but it is more robust because of the larger population and is consistent with signals of benefit in the sickest patients in COVACTA and EMPACTA. The results of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial are eagerly awaited to further inform tocilizumab's role in the management of critically ill patients with covid-19.

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ORIGINAL RESEARCH Nationwide, register based cohort study

Association between use of macrolides in pregnancy and risk of major birth defects

Andersson NW, Olsen RH, Andersen JT

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Study question Is the use of macrolide antibiotics in pregnancy associated with an increased risk of major birth defects?

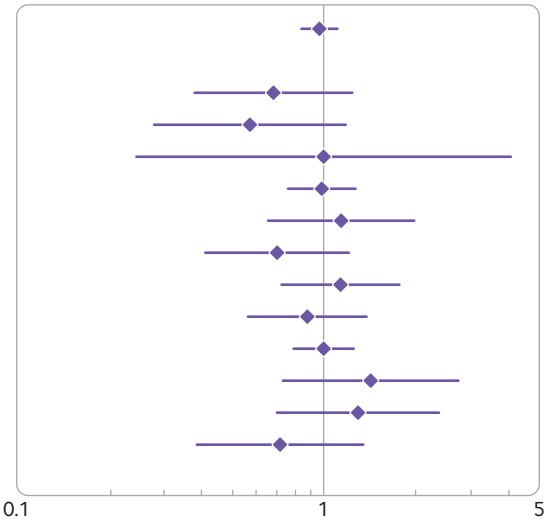
Methods From a Danish nationwide cohort of 1 192 539 pregnancies in 1997-2016, women who had used macrolides during pregnancy were identified (n=13 019) and compared with those who had used penicillin (ie, phenoxymethylpenicillin), matched in a 1:1 ratio on propensity scores, to investigate the risk of major birth defects and specific subgroups of birth defects by relative risk ratio and absolute risk differences. Other comparative groups were women who did not use antibiotics during pregnancy and women who used macrolides recently but before becoming pregnant.

Study answer and limitations This nationwide cohort study found no association between macrolide use in pregnancy and the risk of major birth defects, including for individual macrolides or for subgroups of major birth defects. In matched comparisons, 457 infants were born with major birth defects to women who had used macrolides during pregnancy (35.1 per 1000 pregnancies) compared with 481 infants (37.0 per 1000 pregnancies) born to women who had used penicillin (relative risk ratio 0.95, 95% confidence interval 0.84 to 1.08). The risk of major birth defects was not significantly increased for women who had used macrolides during pregnancy compared with those who had used macrolides recently but before becoming pregnant (relative risk ratio 1.00, 95% confidence interval 0.88 to 1.14) or compared with those who did not use any antibiotics (1.05, 0.95 to 1.17). Study weaknesses were that the definition of use implied that a filled prescription was equivalent to use of the drug and that the risk of residual confounding could not be fully excluded.

What this study adds The study suggests that the use of macrolide antibiotics in pregnancy does not increase the risk of major birth defects. In absolute terms, the findings were inconsistent with an excess of incidences of any major birth defects of more than 2.7 per 1000 among women who used macrolides during pregnancy compared with those who used penicillin.

Funding, competing interests, and data sharing The study received no specific funding. The authors have no competing interests. No additional data available.

Outcome	Macrolides	Comparative group	Relative risk (95% CI)
Macrolides *v* penicillin	**(n=13 017) No of defects**	**(n=13 017) No of defects**	
Any major birth defect	457	481	0.95 (0.84 to 1.08)
Subgroups of birth defects			
Nervous system	19	28	0.68 (0.38 to 1.21)
Eye	12	21	0.57 (0.28 to 1.16)
Face, ear, and neck	4	4	1.00 (0.25 to 4.00)
Heart	127	129	0.98 (0.77 to 1.26)
Orofacial cleft	27	24	1.13 (0.65 to 1.95)
Digestive system	23	33	0.70 (0.41 to 1.19)
Urinary system	43	38	1.13 (0.73 to 1.75)
External genital organs	37	42	0.88 (0.57 to 1.37)
Limbs	138	138	1.00 (0.79 to 1.26)
Musculoskeletal system	21	15	1.40 (0.72 to 2.71)
Respiratory system	23	18	1.28 (0.69 to 2.37)
Other major birth defects	17	24	0.71 (0.38 to 1.32)
Macrolides *v* recent use	**(n=11 908)**	**(n=11 908)**	



Association between the use of macrolides during pregnancy and the risk of major birth defects. The associated risk of major birth defects and specific subgroups of birth defects in women who used macrolides in the first trimester was compared with those who had used penicillin (ie, phenoxymethylpenicillin), matched in a 1:1 ratio on propensity scores