laws-regs/regulations/standardnumber/1910/1910.134AppA. . [Accessed 11 May 2020]
8. Degesys NF, Wang RC, Kwan E, Fahimi J, Noble JA, Raven MC. Correlation between N95 extended use and reuse and fit failure in an emergency department. *JAMA* 2020. https://doi.org/10.1001/jama.2020.9843. . [Accessed 4 June 2020]

doi: 10.1016/j.bja.2020.06.023
Advance Access Publication Date: 26 June 2020

The SARS-CoV-2 effect: an opportunity to reduce general anaesthesia rates for Caesarean section?

Thomas Dixon, Kailash Bhatia* and Malachy Columb

Manchester, UK

*Corresponding author. E-mail: kailash.bhatia@mft.nhs.uk

Keywords: Caesarean section; COVID-19; general anaesthesia; neuraxial anaesthesia; quality improvement

Editor—Caesarean section is the most commonly performed surgical procedure in obstetrics. Evidence from the Hospital Episode Statistics and anaesthetic survey of the National Health Service activity collected as part of the accidental awareness during general anaesthesia (5th National Audit Project [NAP5]) suggests that 8–10% of all Caesarean sections performed in UK utilise a general anaesthetic.[1,2] The WHO declared a global pandemic of coronavirus disease 2019 (COVID-19) in March 2020.[3] Since the onset of COVID-19, recommendations suggest the use of neuraxial anaesthesia if possible over general anaesthesia for Caesarean section to avoid the risks of aerosolisation associated with tracheal intubation and extubation.[4,5] General anaesthesia for Caesarean section in the current pandemic poses risks for all healthcare staff and can impact utilisation of personal protective equipment for the hospital. We investigated whether general anaesthesia rates at our tertiary obstetric unit (10 000 deliveries and 2600 Caesarean sections annually) had changed since March 2020 with the emergence of COVID-19.

Anaesthetic information for all Caesarean sections undertaken at our unit between April 1, 2020 and May 31, 2020 was reviewed from electronic records. We specifically looked to determine the general anaesthesia rate for different categories of Caesarean section (proposed by the Royal College of Obstetricians and Gynaecologists) within that period.[6] We then compared the general anaesthesia rates with the similar period in the preceding 2 yr (2018 and 2019). No ethical approval was needed as the review was classed as an audit as per the Royal College of Anaesthetists (RCoA) standards.[7] Data are presented as frequency (%) and analysed using χ^2 independence, Fisher's expanded exact *P*-values, percentage difference, and 95% confidence interval (CI) with $P<0.05$ (two sided) as significant.

The number of Caesarean sections increased by 4.3% (95% CI: 1.3–7.4; $P=0.015$) during the 2020 period (Table 1). There was a change in rates of general anaesthesia ($P=0.0042$). The rate for the previous 2 yr was 7.5%, and this decreased significantly to 3.3% in 2020, representing a reduction of 4.2% (95% CI: 1.7–6.6; $P=0.0016$) during the pandemic. There was a change in the distribution of general anaesthesia rates in categories with respect to the total number of Caesarean sections ($P=0.022$). There was also a change in the distribution of categories for Caesarean section with respect to delivery rates ($P=0.037$). General anaesthesia rates stratified by category suggest reductions for Categories 2 and 3 Caesarean sections ($P<0.05$). Nine of the 459 Caesarean sections tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1.96%), and all of them had neuraxial anaesthesia. Our hospital met all the RCoA suggested standards for general anaesthesia rates, both before (2018–9) and during the SARS-CoV-2 pandemic.

Our single-centre audit is one of the first to highlight a reduction in the frequency of administration of general anaesthesia for all categories of Caesarean section during the pandemic. The significant change in distribution of general anaesthesia rates for Caesarean section possibly suggests greater awareness of risks posed by an aerosol-generating procedure amongst multidisciplinary obstetric team members, thereby influencing obstetric and anaesthetic decision-making for Caesarean section.

The reduction in general anaesthesia for Caesarean section during the pandemic could also be attributed to staffing changes introduced in our tertiary unit. Since the pandemic began, a 24/7 on-site anaesthetic consultant was established to support on-site anaesthetic trainees. A previous national survey of anaesthetic activity in obstetrics (NAP5) revealed that anaesthesia for 23% of Category 1 Caesarean sections in the UK was delivered by trainees out of hours with distant supervision possibly contributing to the high 'avoidable' general anaesthesia rates.[2] We feel that the staffing changes introduced have led to: (i) enhanced situational awareness, team working, and communication with obstetricians, leading to appropriate and timely decision-making for Caesarean section; and (ii) improved direct and indirect supervision of anaesthetic trainees providing them with more educational and training opportunities to improve both their general

Table 1 Rates of deliveries, general anaesthesia, and categories of Caesarean sections from April 1 to May 31, 2020. Data presented as *n* (%). *†Fisher's expanded *P*-values are presented. ‡Categories of Caesarean section 1–4 are percentages of total number deliveries per year (n=4300; χ^2: 16.04; degrees of freedom: 8). ¶General anaesthesia rates in Categories 1–4 are based on the total Caesarean sections per year (n=1329; Fisher's expanded exact). §General anaesthesia rates are percentages stratified in each category (Fisher's expanded exact test).

Year	2018	2019	2020	P-value
Deliveries total, *n*	1484	1461	1355	
Caesarean section total	431 (29.0)	439 (30.1)	459 (33.9)	0.015*
General anaesthesia total	29 (6.7)	36 (8.2)	15 (3.3)	0.0042†
Categories 1–4 Caesarean section				0.037‡
General anaesthesia in Categories 1–4 Caesarean section				0.022¶
Category 1				
Caesarean section	116 (7.7)	126 (8.6)	105 (7.7)	
General anaesthesia	15 (12.9)	22 (17.5)	12 (11.4)	0.41§
Category 2				
Caesarean section	81 (5.5)	77 (5.2)	103 (7.6)	
General anaesthesia	4 (4.9)	8 (10.4)	2 (1.9)	0.044§
Category 3				
Caesarean section	30 (2.0)	26 (1.8)	37 (2.7)	
General anaesthesia	4 (13.3)	1 (3.8)	0 (0.0)	0.045§
Category 4				
Caesarean section	204 (13.7)	210 (14.4)	214 (15.8)	
General anaesthesia	6 (2.9)	5 (2.4)	1 (0.5)	0.12§

anaesthesia and neuraxial anaesthesia techniques and decreased failure rates.

General anaesthesia rates for Caesarean section have declined markedly in the developed world over the last two decades. We feel COVID-19 has given obstetric anaesthetists in our tertiary unit an opportunity to drive down general anaesthesia rates for Caesarean section further, as is evident from our audit. Previous studies have highlighted that general anaesthesia for Caesarean section, with known risks of difficult or failed intubation, aspiration, and accidental awareness, is associated with a higher maternal mortality and morbidity (increased blood transfusion, surgical site infection, pain, venous thromboembolism, and length of stay) especially when undertaken in an emergency setting.[8,9] Thus, a safe reduction in general anaesthesia rate for Caesarean section (partly caused by COVID-19) is desirable, is in the 'best interests of mothers', and is a welcome sign for all personnel in the operating theatre environment who may feel vulnerable during an aerosol-generating procedure. Whether anaesthetists can sustain this reduction in general anaesthesia rates, and translate this reduction into improving maternal outcomes and morbidity needs to be researched further.

We recommend that all obstetric units monitor their general anaesthesia rates for Caesarean section as part of quality improvement programmes. Changes in rate can then lead to analysis of contributory factors and quantification of changes in maternal morbidity and mortality associated with the general anaesthesia rates.

Declarations of interest

MC has editorial board roles with the *European Journal of Anaesthesiology*, *British Journal of Anaesthesia*, and *International Journal of Obstetric Anesthesia*. No other conflicts of interest exist.

References

1. Health & Social Care Information Centre. Hospital Episode Statistics: NHS maternity statistics 2012–2013. Available from: https://files.digital.nhs.uk/publicationimport/pub12xxx/pub12744/nhs-mate-eng-2012-13-summ-repo-rep.pdf, Accessed 1 June 2020.
2. Sury MRJ, Palmer JHMG, Cook TM, Pandit JJ. The state of UK anaesthesia: a survey of National Health Service activity in 2013. *Br J Anaesth* 2014; **113**: 575–84
3. World Health Organization. *Rolling updates on coronavirus disease (COVID-19)*. Geneva, Switzerland: World Health Organization; 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. [Accessed 1 June 2020]
4. Uppal V, Sondekoppam RV, Lobo CA, Kolli S, Kalagara HKP. *Practice recommendations on neuraxial anesthesia and peripheral blocks during the COVID-19 pandemic* 2020. Available from: www.asra.com/covid-19/raguidance. [Accessed 1 June 2020]
5. Bampoe S, Odor PM, Lucas N. Novel coronavirus SARS-CoV-2 and COVID-19. Practice recommendations for obstetric anaesthesia: what we have learned thus far. *Int J Obstet Anaesth* 2020; **43**: 1–8
6. Royal College of Obstetricians and Gynaecologists. *Classification of urgency of Caesarean section—a continuum of risk (Good Practice No. 11)* 2010. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/goodpractice11classificationofurgency.pdf. [Accessed 5 June 2020]
7. Colvin JR, Peden CJ. *Raising the standard: a compendium of audit recipes for continuous quality improvement in anaesthesia*. 3rd Edn. London: Royal College of Anaesthetists; 2012
8. Sobhy S, Zamora J, Dharmarajah K, et al. Anaesthesia-related maternal mortality in low-income and middle-

income countries: a systematic review and meta-analysis. *Lancet Glob Health* 2016; **4**. e320–7
9. Guglielminotti J, Landau R, Li G. Adverse events and factors associated with potentially avoidable use of general anesthesia in cesarean deliveries. *Anesthesiology* 2019; **130**: 912–22

doi: 10.1016/j.bja.2020.06.021
Advance Access Publication Date: 19 June 2020

Inclusion of pregnant women in clinical trials of COVID-19 therapies: what have we learned?

Sharon Einav[1], Mariachiara Ippolito[2] and Andrea Cortegiani[2,*]

[1]Jerusalem, Israel and [2]Palermo, Italy

*Corresponding author. E-mail: andrea.cortegiani@unipa.it

Keywords: clinical trial; COVID-19; drug development; pregnancy; randomised controlled trial

Editor—The Intensive Care National Audit and Research Centre (ICNARC) report from more than 200 ICUs in England, Wales, and Northern Ireland showed that 2.8% of critically ill coronavirus disease 2019 (COVID-19) patients were currently pregnant or had been pregnant recently.[1] A systematic review of COVID-19 occurring during pregnancy (n=108) also reported 'severe maternal morbidity as a result of COVID-19'.[2] Observational studies describing infected pregnant women noted worsening hypoxaemia of clinical concern. Pulmonary infiltrates were described in 79% of the pregnant women with COVID-19 in the Wuhan cohort. The Italian cohort described pneumonia in 45% and ICU admission for 9% of pregnant women.[3] There have been also case reports of severe COVID-19 related cardiomyopathy, multiorgan failure, and deaths in pregnant women.[4,5]

As the *COVID-19* pandemic spreads globally, an increasing number of patients are receiving experimental treatments, some within the framework of RCTs and others as off-label or compassionate use. Off-label or compassionate drug treatment is provided in the face of a life-threatening disease with no proven treatment, that is clinical equipoise exists regarding treatment. The justifications for compassionate use of investigational drugs include both the contribution of data (efficacy, safety) for the benefit of future patients and possible benefits to the patient enrolled. The European Medical Agency (EMA) Guideline on Compassionate Use of Medicinal Products clearly states that compassionate use is performed primarily for therapeutic purposes. Thus off-label or compassionate use of medication is theoretically justified also in pregnant women.

Inclusion of pregnant women in clinical trials is more challenging. Until the 1990s, women were almost categorically excluded from participating in clinical trials solely for being pregnant or even of childbearing age. The disastrous experiences with diethylstilboestrol and thalidomide entrenched concerns regarding potential fetal harm. However, since the 1993 Council for International Organizations of Medical Sciences declared that exclusion of women from participation in clinical trials is unjust, this approach is no longer acceptable. The EMA and the US Institute of Medicine both endorse fair enrolment of any woman eligible for participation in clinical research. The US Food and Drug Administration states that 'investigational drugs may be used in pregnant women if adequate non-clinical studies (including studies on pregnant animals) have been completed and there is a prospect of direct benefit to the pregnant woman and/or fetus',[6] and the US National Institute of Health 'strongly encourages including pregnant women in clinical research in all circumstances in which their inclusion is scientifically valid and ethically permissible'.[7]

A recent editorial on drug use during pandemics stated that the 'tragedy of not discovering new therapies during an outbreak cannot be repeated'.[8] It also elaborated that 'By participating in an RCT, both patients and clinicians can benefit from the unique opportunity to directly contribute to the discovery of new therapies'. However, there is ongoing tension between the bioethical and research consensus that pregnant women should be included in clinical trials and actual implementation of such inclusion in a reality where one in four medical lawsuits may be an obstetric case. We studied the approach towards recruitment of pregnant women to interventional clinical trials for COVID-19. To this end, we searched the US National Library of Medicine registry (Clinicaltrial.gov) for studies including the terms '*COVID* OR *coronavirus* OR *SARS-COV-2*' up to April 15, 2020. Overall, 630 registered trials were identified. After applying a filter for study type ('interventional' trials), we identified 401 trials which were retrieved and screened. Duplicate trials, withdrawn or suspended trials, and trials unrelated to the COVID-19 pandemic were excluded. The data on the final 371 included trials are presented in Table 1. Among the 371 interventional trials registered, most declare pregnancy an exclusion criterion (251/371, 68%). This is most striking in trials investigating the use of drugs (235/310, 75.8%). Many trials altogether avoid mention of pregnant women in their inclusion/exclusion criteria (117/371, 31%). Several trials (including those on the use of chloroquine) suggest referring to 'known'