

**Contraceptive failure and sugammadex administration: Surveys of professional knowledge and practice**

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Editor,

While the global popularity of sugammadex continues to rise,<sup>1</sup> anaesthetists' knowledge and management of an important potential interaction may have failed to keep pace.<sup>2</sup> In-vitro studies (isothermal microcalorimetry) have identified high binding affinity of sugammadex for steroidal hormones, notably progesterone.<sup>3</sup> As the active component of many hormonal contraceptives, in vivo inactivation of progesterone by sugammadex could therefore temporarily cause contraceptive failure, exposing women to the risk of unplanned pregnancy.<sup>4</sup>

The true incidence of unplanned pregnancy due to this interaction is unknown, with no in-vivo or prospective clinical trials published or recorded by the manufacturer Merck, and no relevant warnings identified on our search of United Kingdom (U.K.) Medicines and Healthcare products Regulatory Agency (MHRA) and United States (U.S.) food and drug administration (FDA) databases. In a retrospective audit (of 1000 patients receiving sugammadex) out of the 134 women using hormonal contraception at the time of receiving sugammadex, one unintended pregnancy (incidence 0.7%, 95% CI 0.0, 4.1) was identified.<sup>5</sup> In the absence of reliable data manufacturers advice is therefore cautionary, recommending risk-counselling of women of childbearing age, 'missed pill rules' for women taking oral hormonal contraceptives, and additional non-hormonal contraceptive use for 7 days in women using non-oral contraceptives (vaginal rings, implants, and intra-uterine devices).<sup>4</sup>

Merck include this as part of their prescribing information and individual hospitals have created their own patient information leaflets and letters,<sup>6-9</sup> but risk counselling and information provision have been shown to be rare and awareness of the interaction among anaesthetic professionals variable.<sup>5,9</sup>

In a two-stage study, we surveyed knowledge of the potential interaction between sugammadex and contraceptives among professionals and investigated perioperative counselling practices and the provision of information at a metropolitan teaching hospital. We hypothesised that awareness of the risk of contraceptive failure would be low, and that at-risk women would infrequently be counselled.

Anaesthetists and physician associates working at four University College London Hospitals (UCLH) sites (University College Hospital, Westmoreland Street, Grafton Way Building, and the Royal National ENT Hospital) were invited to anonymously complete a purpose-built questionnaire (Supplementary file 1), comprising 7 questions on patterns of use and knowledge of side effects. The survey had been pilot tested by a small (n=5) representative sample of anaesthetists. Invitations were distributed weekly for four weeks via departmental communications, and posters displaying a QR weblink were prominently placed. As our intention to analyse aggregate responses was explicitly stated, consent was implied by participation. The questionnaire was completed by 82 (54%) professionals. Sugammadex administration was frequent, with more than 40% of anaesthetists administering the drug at least 1-2 times every week, and widespread, with 90% of respondents reporting administering it to patients on elective and emergency theatre lists. While knowledge of contraceptive failure risk was near universal (94%), 70% reported not counselling women of childbearing age for contraceptive failure.

Our retrospective 6-week review of sugammadex use was conducted across all UCLH theatres, except labour ward and neurosurgical theatres. The project was approved by the departmental Audit Lead on 29<sup>th</sup> April 2021. We identified patients who had received sugammadex, from locally mandated logbooks, and retrieved their electronic notes to determine, sex, age, and surgical specialty. The perioperative care records of women of childbearing age were then reviewed to determine if counselling for contraceptive failure was warranted, and if it had been documented. Women of childbearing age were defined as females aged 12-55 years, and cases excluded if their history included hysterectomy and or bilateral salpingo-oophorectomy (BSO), or inpatient surgery included hysterectomy, surgical termination of pregnancy, or BSO or treatment of ectopic pregnancy or evacuation of retained products of conception. In total 234 patients received sugammadex, of whom 48 (28%) were women of childbearing age, meeting our criteria for counselling. Documentation of discussion of potential contraceptive failure, or information provision was absent from every one of these 48 patient records.

In response to these findings, we are developing a series of local solutions for each stage of the peri-operative journey (Figure 1). Pre-operatively, counselling is encouraged by specific inclusion of this

outcome in consent for anaesthesia. Intra-operative sugammadex charting will prompt an alert in at-risk patients, reminding anaesthetists to enact post-operative measures. Post-operatively information is delivered verbally, as a take-home leaflet, and by letter to improve postoperative recall.<sup>10</sup> These measures have been supported by education of relevant staff groups and we plan to re-audit practice.

Our single-centre study contributes to the growing literature showing that, despite knowledge of the potential for contraceptive failure due to sugammadex among anaesthetic professionals, appropriate counselling of and provision of information to at-risk women remain rare.<sup>5-9</sup> Existing estimates of the incidence of unplanned pregnancy due to sugammadex administration may underestimate reality since, due to poor information provision, women may be unaware of the cause of contraceptive failure. Nevertheless, the consequences of this interaction are far-reaching and the sugammadex use is expected to increase dramatically when the drug comes off patent in coming years (2023 in U.K. and Europe and 2026 in the U.S.).<sup>11</sup>

We therefore argue that a co-ordinated national approach is now needed, to better inform women of the potential risks of sugammadex administration and to attempt to quantify the incidence of unplanned pregnancy due to the interaction with progesterone-based contraceptives. The inequity in the provision of healthcare to women is a known reality and one which has gathered recent attention. Unfortunately, all too often problems fade from public discussion without a resolution. Previous warnings regarding the use of sugammadex in women of childbearing age,<sup>5,9</sup> have suffered a similar fate and a response from the specialty is now required. We suggest that national guidance and the sharing of available resources is actioned. Ultimately, ensuring women can safely receive sugammadex as part of a general anaesthetic is a small but necessary step in helping to remove inequalities in women's health. Future research, may include a prospective in-vivo trial whereby serial serum sampling of progesterone concentrations before and after sugammadex administration, in women using hormonal contraceptives and undergoing elective surgical procedures, to help quantify the risk of unplanned pregnancy.

Limitations of our study include a lack of follow-up of women to enquire about unintended pregnancy and the absence of a re-audit to see if our interventions have yet been effective.

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**Figure 1: Safety innovations: A perioperative approach to safeguard women of childbearing age receiving Sugammadex at UCLH**

