CPD BULLETIN

ACADEMY OF MEDICINE, SINGAPORE | 2021 SEPTEMBER (2)

Foreword

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This issue of the CPD Bulletin is focused on Obstetrics and Gynaecology, and I know our O&G Fellows will welcome it for the bite sized précis of the recent scientific papers curated across the various O&G subspecialties, given our very busy work schedules and particularly during these pandemic times.

Top on the list in my opinion would be the articles on COVID-19 and vaccination in pregnancy. This is required reading for all obstetricians who must surely be inundated with questions from concerned mothers-to-be about being vaccinated. The importance for all obstetricians to be *au fait* with the scientific literature and to be able to be correct counselling on COVID-19 vaccination in pregnancy cannot be over-emphasized.

The other articles are also extremely useful as they cover practical clinical issues encountered in everyday practice. These include the place of pre-conception aspirations and fertility, to objective comparative information of levonorgestrel and copper intrauterine devices which clinicians will find invaluable for counselling their patients seeking emergency contraception. There is also reassuring data on the risk of fertility treatment on breast cancer, the utility of a non-surgical treatment for HSIL, the surprising finding of family history as a predictor of current preterm birth, and the results of using a high dose oxytocin augmentation regimen in nulliparous women.

I hope that these papers will interest and possibly intrigue our readers, stimulating discussions, debates, and journal clubs with a view towards reviewing their current practice. I wish you all a happy and fruitful perusal of this issue.

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COVID-19

	ARTICLES
1	**Antibody Response to Coronavirus Disease 2019 (COVID-19) Messenger RNA Vaccination in Pregnant Women and Transplacental Passage Into Cord Blood** FULL ARTICLE ACCESS *Prabhu M, Murphy EA, Sukhu AC, Yee J, Singh S, Eng D, Zhao Z, Riley LE, Yang YJ.* **Obstet Gynecol. 2021 Aug 1;138(2):278-280.** *PMID: 33910219* Coronavirus disease 2019 (COVID-19) vaccination in pregnancy induces a robust maternal immune response, with transplacental antibody transfer detectable in cord blood as early as 16 days after the first dose.
2	**Severe acute respiratory syndrome coronavirus 2 serology levels in pregnant women and their neonates** FULL ARTICLE ACCESS *Kubiak JM, Murphy EA, Yee J, Cagino KA, Friedlander RL, Glynn SM, Matthews KC, Jurkiewicz M, Sukhu AC, Zhao Z, Prabhu M, Riley LE, Yang YJ.* **Am J Obstet Gynecol. 2021 Jul;225(1):73.e1-73.e7.** *PMID: 33497654* A total of 88 serology positive pregnant women were included in this study. The antibody levels were higher in symptomatic pregnant women than in asymptomatic pregnant women. Serology studies in 34 women with symptom onset data revealed that the maternal immunoglobulin M and immunoglobulin G levels peak around 15 and 30 days after the onset of coronavirus disease 2019 symptoms, respectively. Furthermore, studies of 50 neonates born to this subset of serology positive women showed that passive immunity in the form of immunoglobulin G is conferred in 78% of all neonates. The presence of passive immunity is dependent on the maternal antibody levels, and the levels of neonatal immunoglobulin G correlate with maternal immunoglobulin G levels. The maternal immunoglobulin G levels and maternal use of oxygen support were predictive of the neonatal immunoglobulin G levels. We demonstrated that maternal serologies correlate with symptomatic maternal infection, and higher levels of maternal antibodies are associated with passive neonatal immunity. The maternal immunoglobulin G levels and maternal use of oxygen support, a marker of disease severity, predicted the neonatal immunoglobulin G levels. These data will further guide the screening for this uniquely linked population of mothers and their neonates and can aid in developing maternal vaccination strategies.

PRACTICE-CHANGING UPDATES

ARTICLES

1 **The Effect of Preconception-Initiated Low-Dose Aspirin on Human Chorionic Gonadotropin-Detected Pregnancy, Pregnancy Loss, and Live Birth: Per Protocol Analysis of a Randomized Trial** FULL ARTICLE ACCESS

Naimi AI, Perkins NJ, Sjaarda LA, Mumford SL, Platt RW, Silver RM, Schisterman EF.
Ann Intern Med. 2021 May;174(5):595-601.
PMID: 33493011

A previous large, randomized trial indicated that preconception-initiated low-dose aspirin (LDA) therapy did not have a positive effect on pregnancy outcomes. However, this trial was subject to nonadherence, which was not taken into account by the intention-to-treat approach.

The objective is to estimate per protocol effects of preconception initiated LDA on pregnancy loss and live birth. The EAGeR (Effects of Aspirin on Gestation and Reproduction) trial was used to construct a prospective cohort for a post hoc analysis. (ClinicalTrials.gov: NCT00467363). 4 university medical centres in the United States were used in the setting. 1227 women between the ages of 18 and 40 years who had 1 or 2 previous pregnancy losses and were attempting pregnancy. Adherence to LDA or placebo, assessed by measuring pill bottle weights at regular intervals during follow-up. Primary outcomes were human chorionic gonadotropin (hCG)-detected pregnancies, pregnancy losses, and live births, determined by pregnancy tests and medical records. Relative to placebo, adhering to LDA for 5 of 7 days per week led to 8 more hCG-detected pregnancies (95% CI, 4.64 to 10.96 pregnancies), 15 more live births (CI, 7.65 to 21.15 births), and 6 fewer pregnancy losses (CI, -12.00 to -0.20 losses) for every 100 women in the trial. In addition, compared with placebo, post-conception initiation of LDA therapy led to a reduction in the estimated effects. Furthermore, effects were obtained in a minimum of 4 of 7 days per week.

The EAGeR trial data for this study were analysed as observational data, thus are subject to the limitations of prospective observational studies. Per protocol results suggest that preconception use of LDA at least 4 days per week may improve reproductive outcomes for women who have had 1 or 2 pregnancy losses. Increasing adherence to daily LDA seems to be key to improving effectiveness.

2 **Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception** FULL ARTICLE ACCESS

Turok DK, Gero A, Simmons RG, Kaiser JE, Stoddard GJ, Sexsmith CD, Gawron LM, Sanders JN.
N Engl J Med. 2021 Jan 28;384(4):335-344.
PMID: 33503342

In the United States, more intrauterine device (IUD) users select levonorgestrel IUDs than copper IUDs for long-term contraception. Currently, clinicians offer only copper IUDs for emergency contraception because data are lacking on the efficacy of the levonorgestrel IUD for this purpose.

This randomized noninferiority trial, in which participants were unaware of the group assignments, was conducted at six clinics in Utah and included women who sought emergency contraception after at least one episode of unprotected intercourse within 5 days before presentation and agreed to placement of an IUD.

We randomly assigned participants in a 1:1 ratio to receive a levonorgestrel 52-mg IUD or a copper T380A IUD. The primary outcome was a positive urine pregnancy test 1 month after IUD insertion. When a 1-month urine pregnancy test was unavailable, we used survey and health record data to determine pregnancy status. The prespecified noninferiority margin was 2.5 percentage points. Among the 355 participants randomly assigned to receive levonorgestrel IUDs and 356 assigned to receive copper IUDs, 317 and 321, respectively, received the interventions and provided 1-month outcome data. Of these, 290 in the levonorgestrel group and 300 in the copper IUD group had a 1-month urine pregnancy test. In the modified intention-to-treat and per-protocol analyses, pregnancy rates were 1 in 317 (0.3%; 95% confidence interval [CI], 0.01 to 1.7) in the levonorgestrel group and 0 in 321 (0%; 95% CI, 0 to 1.1) in the copper IUD group; the between-group absolute difference in both analyses was 0.3 percentage points (95% CI, -0.9 to 1.8), consistent with the noninferiority of the levonorgestrel IUD to the copper IUD. Adverse events resulting in participants seeking medical care in the first month after IUD placement occurred in 5.2% of participants in the levonorgestrel IUD group and 4.9% of those in the copper IUD group.

The levonorgestrel IUD was noninferior to the copper IUD for emergency contraception.

FEATURED ARTICLES

	ARTICLES
1	**Risk of breast cancer in women treated with ovarian stimulation drugs for infertility: a systematic review and meta-analysis** FULL ARTICLE ACCESS *Beebeejaun Y, Athithan A, Copeland TP, Kamath MS, Sarris I, Sunkara SK.* **Fertil Steril. 2021 Jul;116(1):198-207.** *PMID: 34148584* The objective is to evaluate the evidence addressing the association between the use of ovarian stimulation drugs and the risk of breast cancer. Systematic review and meta-analysis. The patients are women without any previous history of breast cancer undergoing ovarian stimulation. Electronic databases were searched from 1990 until January 2020. All cohort studies reporting new incidences of breast cancer in infertile women using ovarian stimulating drugs were included. Treated (exposed) infertile women were compared with the unexposed general population with unexposed infertile women as controls. New diagnosis of breast cancer within an infertile and general population after exposure to ovarian stimulation drugs. Overall, the quality of evidence was very low because of the serious risk of bias and indirectness (nonrandomized studies). There was no significant increase in the risk of breast cancer among women treated with any ovarian stimulation drug for infertility compared with that in unexposed controls from the general population and the infertile population (pooled odds ratio 1.03, 95% Confidence interval 0.86 to 1.23, 20 studies, I2 = 88.41%, very low quality of evidence). Furthermore, no significant increase in the risk of breast cancer was found with the use of clomiphene citrate or gonadotropins, alone or in combination. The current study found that the use of clomiphene citrate and gonadotropins in infertile women was not associated with an increased risk of breast cancer.
2	**Prenatally diagnosed omphaloceles: Report of 92 cases and association with Beckwith-Wiedemann syndrome** FULL ARTICLE ACCESS *Abbasi N, Moore A, Chiu P, Ryan G, Weksberg R, Shuman C, Steele L, Chitayat D.* **Prenat Diagn. 2021 Jun;41(7):798-816.** *PMID: 33687072* The objective is to describe the prevalence, perinatal and long-term outcomes of Beckwith-Wiedemann syndrome (BWS) among prenatally detected omphaloceles. All prenatally diagnosed omphaloceles from 2010 to 2015 within a single tertiary care centre were identified. An echocardiogram and detailed fetal ultrasound were performed, and amniocentesis was offered with karyotype/microarray analysis and BWS molecular testing. Perinatal, neonatal, and long-term outcomes were retrieved for BWS cases. Among 92 omphaloceles, 62 had additional anomalies. Abnormal karyotypes were identified in 23/62 (37%) non-isolated and 2/30 (7%) isolated cases. One BWS case (5%) was identified among non-isolated omphaloceles and six BWS cases (37.5%) were identified among isolated omphaloceles after exclusion of aneuploidy. Among 19 BWS cases, 21% were conceived by ART. All omphaloceles underwent primary closure. Prenatally, macrosomia and polyhydramnios were seen in 42%. Macroglossia and nephromegaly were more commonly detected postnatally. Preterm birth occurred in 10/19 (53%) cases and cesarean deliveries were performed in 7/19 (40%) cases. Overall mortality was 20% (4/19). Embryonal tumors were diagnosed in 2/16 (12.5%) children, and neurodevelopmental outcomes were normal in 9/12 (75%) survivors. After excluding aneuploidy, BWS was identified in 37.5% and 5% of isolated and non-isolated omphaloceles, respectively. Omphaloceles were small-moderate size with good long-term surgical and neurodevelopmental outcomes when isolated.

3 **Topical Imiquimod for the Treatment of High-Grade Squamous Intraepithelial Lesions of the Cervix: A Randomized Controlled Trial** FULL ARTICLE ACCESS

Fonseca BO, Possati-Resende JC, Salcedo MP, Schmeler KM, Accorsi GS, Fregnani JHTG, Antoniazzi M, Pantano NP, Santana IVV, Matsushita GM, Dos Reis R.

Obstet Gynecol. 2021 Jun 1;137(6):1043-1053.

PMID: 33957649

The objective is to evaluate the histologic response rate of high-grade squamous intraepithelial lesions (HSIL) of the cervix after topical application of 5% imiquimod cream. In this phase II trial, women with cervical HSIL (cervical intraepithelial neoplasia [CIN] 2-3) were randomly assigned to 250 mg of 5% imiquimod cream applied to the cervix weekly for 12 weeks, followed by loop electrosurgical excision procedure (LEEP) without preceding treatment.

The sample size was calculated based on the HSIL regression rates previously reported by Grimm et al. The primary outcome was rate of histologic regression (to CIN 1 or less) in LEEP specimens. Prespecified secondary endpoints included surgical margin status and adverse events. Outcomes were stratified by human papillomavirus type and lesion grade (CIN 2 or CIN 3). Results were reported according to per protocol (PP) and intention-to-treat (ITT) analyses. Ninety women were enrolled: 49 in the experimental group and 41 in the control group. In the PP population, histologic regression was observed in 23 of 38 participants (61%) in the experimental group compared with 9 of 40 (23%) in the control group (P=.001). Surgical margins were negative for HSIL in 36 of 38 participants (95%) in the experimental group and 28 of 40 (70%) in the control group (P=.004). In the ITT population, rates of histologic regression also were significantly higher in the experimental group. Rates of adverse events in the experimental group were 74% (28/38) in the PP population and 78% (35/45) in the ITT population. Adverse events were mild, with abdominal pain being the most common. Three patients in the experimental group had grade 2 adverse events, including vaginal ulcer, vaginal pruritus with local edema, and moderate pelvic pain.

Weekly topical treatment with imiquimod is effective in promoting regression of cervical HSIL.

4 **High-Dose Compared with Standard-Dose Oxytocin Regimens to Augment Labour in Nulliparous Women: A Randomized Controlled Trial**

Son M, Roy A, Stetson BT, Grady NT, Vanecko MC, Bond N, Swanson K, Grobman WA, Miller ES, Peaceman AM.

Obstet Gynecol. 2021 Jun 1;137(6):991-998.
PMID: 33957657

The objective is to evaluate whether a high-dose oxytocin regimen reduces the risk for primary caesarean birth and other obstetric morbidities when compared with standard dosing.

In a double-blind randomized clinical trial of nulliparous women at or beyond 36 weeks of gestation who were undergoing augmentation of labour, participants were assigned to high-dose (initial and incremental rates of 6 milliunits/min) or standard-dose (initial and incremental rates of 2 milliunits/min) oxytocin regimens. The primary outcome was caesarean birth. Prespecified secondary outcomes included labour duration, clinical chorioamnionitis, endometritis, postpartum haemorrhage, Apgar score 3 or less at 5 minutes, umbilical artery acidaemia, neonatal intensive care unit admission, perinatal death, and a severe perinatal morbidity composite.

A sample size of 501 per group (n=1,002) was planned to detect a 6.6% absolute reduction in rate of the primary outcome, from 20% in the standard-dose group to 13.4% in the high-dose group with 80% power. From September 2015 to September 2020, 1,003 participants were randomized-502 assigned to high-dose and 501 assigned to standard dosing. The majority of participants were of White race, were married or living as married, and had commercial insurance. Baseline characteristics between groups were similar. The primary outcome occurred in 14.5% of those receiving high-dose compared with 14.4% of those receiving standard-dose oxytocin (relative risk, 1.01; 95% CI 0.75-1.37). The high-dose group had a significantly shorter mean labour duration (9.1 vs 10.5 hours; P<.001), and a significantly lower chorioamnionitis incidence (10.4% vs 15.6%; relative risk, 0.67; 95% CI 0.48-0.92) compared with standard dosing. Umbilical artery acidaemia was significantly less frequent in the high-dose group in complete case analysis, but this finding did not persist after multiple imputation (relative risk, 0.55; 95% CI 0.29-1.04). There were no significant differences in other secondary outcomes.

Among nulliparous participants who were undergoing augmentation of labour, a high-dose oxytocin regimen, compared with standard dosing, did not affect the caesarean birth risk but significantly reduced labour duration and clinical chorioamnionitis frequency without adverse effects on perinatal outcomes.

5 **Family history is a predictor of current preterm birth** FULL ARTICLE ACCESS

Koire A, Chu DM, Aagaard K.

Am J Obstet Gynecol MFM. 2021 Jan;3(1):100277.

PMID: 33451608

Reliable prediction of spontaneous preterm birth remains limited, particularly for nulliparous and multiparous women without a personal history of preterm birth. Although previous preterm birth is a risk factor for recurrent preterm birth, most spontaneous preterm births occur in women with no previous history of preterm birth.

This study aimed to determine whether patients' self-reported maternal family history of preterm births among siblings and across 3 generations was an independent risk factor for spontaneous preterm births after controlling for potential confounders. This was a retrospective analysis of a prospectively acquired cohort using a comprehensive single, academic centre database of deliveries from August 2011 to July 2017. The objective of the current analysis was to evaluate the risk of preterm birth among women with and without a family history of preterm birth. All subjects in the database were directly queried regarding familial history across 3 generations, inclusive of obstetrical morbidities. Index subjects with probable indicated preterm birth (e.g., concurrent diagnosis of preeclampsia; haemolysis, elevated liver enzymes, and low platelet count; or placenta previa or placenta accreta) were excluded, as were nonsingleton pregnancies. Univariate and multivariate analyses with logistic regression were used to determine significance and adjusted relative risk. In this study, 23,816 deliveries were included, with 2345 (9.9%) born prematurely (<37 weeks' gestation). Across all subjects, preterm birth was significantly associated with a maternal family history of preterm birth by any definition (adjusted relative risk, 1.44; P<.001), and the fraction of preterm birth occurring in women with a positive family history increased with decreasing gestational age at which the index subjects of preterm birth occurred. For nulliparous women, a history in the subject's sister posed the greatest risk (adjusted relative risk, 2.25; P=.003), whereas for multiparous women with no previous preterm birth, overall family history was most informative (P=.003). Interestingly, a personal history of the index subject herself being born preterm presented the greatest individual risk factor (adjusted relative risk, 1.94; P=.004). Spontaneous preterm birth in the current pregnancy was significantly associated with a maternal family history of preterm birth among female relatives within 3 generations and notably sisters. The risk persisted among gravidae without a previous preterm birth, demonstrating the capacity for familial history to independently predict risk of spontaneous preterm birth even in the context of a negative personal history.

This study provides evidence that self-reported maternal family history is relevant in a US population cohort and across more distant generations than has previously been reported.

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