

## MEDICINE ABSTRACTS

### Chest

*C. R. Bruce et al., Challenges in Deactivating a Total Artificial Heart for a Patient With Capacity Deactivating a Total Artificial Heart, Chest* 145.3 (March 1, 2014): 625–631 • The use of mechanical circulatory support (MCS) devices has increased sixfold since 2006. Although there is an established legal and ethical consensus that patients have the right to withdraw and withhold life-sustaining interventions when burdens exceed benefits, this consensus arose prior to the widespread use of MCS technology and is not uniformly accepted in these cases. There are unique ethical and clinical considerations regarding MCS deactivation. Our center recently encountered the challenge of an awake and functionally improving patient with a total artificial heart (TAH) who requested its deactivation. We present a narrative description of this case with discussion of the following questions: (1) Is it ethically permissible to deactivate this particular device, the TAH? (2) Are there any particular factors in this case that are ethical contraindications to proceeding with deactivation? (3) What are the specific processes necessary to ensure a compassionate and respectful deactivation? (4) What proactive practices could have been implemented to lessen the intensity of this case's challenges? We close with a list of recommendations for managing similar cases.

### Human Reproduction

*G. M. Chambers et al., Hospital Utilization, Costs and Mortality Rates during the First 5 Years of Life: A Population Study of ART and Non-ART Singletons, Hum Reprod* 29.3 (March 2014): 601–610 • *Study Question:* Do singletons conceived following assisted reproduction technologies (ARTs) have significantly different hospital utilization, and therefore costs, compared with non-ART children during the first 5 years of

life? *Summary Answer:* ART singletons have longer hospital birth-admissions and a small increased risk of re-admission during the first 5 years of life resulting in higher costs of hospital care. *What Is Known Already:* ART singletons are at greater risk of adverse perinatal outcomes compared with non-ART singletons. Long-term physical and mental health outcomes of ART singletons are generally reassuring. There is a scarcity of information on health service utilization and the health economic impact of ART conceived children. *Study Design, Size, Duration:* A population cohort study using linked birth, hospital and death records. Perinatal outcomes, hospital utilization and costs, and mortality rates were compared for non-ART and ART singletons to 5 years. Adjustments were made for maternal age, parity, sex, birth year, socioeconomic status and funding source. Australian Diagnosis Related Groups cost-weights were used to derive costs. All costs are reported in 2009/2010 Australian dollars. *Participants/Materials, Setting, Methods:* All babies born in Western Australia between 1994 and 2003 were included; 224,425 non-ART singletons and 2,199 ART conceived singletons. Hospital admission and death records in Western Australia linked to 2008 were used. *Main Results and the Role of Chance:* Overall, ART singletons had a significantly longer length of stay during the birth-admission (mean difference 1.8 days,  $P < 0.001$ ) and a 20% increased risk of being admitted during the first 5 years of life. The average adjusted difference in hospital admission costs up to 5 years of age was \$2,490, with most of the additional cost occurring during the birth-admission (\$1,473). The independent residual cost associated with ART conception was \$342 during the birth-admission and an additional \$548 up to 5 years of age, indicating that being conceived as an ART child

predicts not only higher birth-admission costs but excess costs to at least 5 years of age. *Limitations, Reasons for Caution:* This study could not investigate the impact of different ART practices and techniques on perinatal outcomes or hospital utilization, nor could it adjust for parental characteristics such as cause of infertility and treatment-seeking behaviour. This study related to ART treatment undertaken before 2003. *Wider Implications of the Findings:* Clinicians and patients should be aware of the risk of poorer perinatal outcomes and increased hospitalization of ART singletons compared with non-ART singletons. These differences are significant enough to affect health-care resource consumption, but are substantially and significantly less than those associated with ART multiple birth infants. Understanding the short- and long-term health services and economic impact of ART is important for setting the research agenda in ART, for informing economic evaluations of infertility and treatment strategies, and for providing an important input to clinical and administrative decision making. *Study Funding/Competing Interests:* No specific funding was used to undertake this study and the authors report no conflicts of interest. A number of the authors receive Research Grants to their institutions from the Australian Government. G.M.C. receives grant support to her institution from the Australian Government, Australian Research Council (ARC) Linkage Grant No LP1002165; ARC Linkage Grant Partner Organisations are IVFAustralia, Melbourne IVF and Queensland Fertility Group. V.P.H. is employed as an Economics Research Associate on the same grant.

*A. T. Hansen et al., Increased Venous Thrombosis Incidence in Pregnancies after In Vitro Fertilization, Hum Reprod* 29.3 (March 2014): 611–617 • *Study Question:* Is venous thrombosis risk increased in pregnancies after in vitro fertilization? *Summary Answer:* The venous thrombosis incidence was significantly increased in pregnancies after in vitro fertilization; especially in the first trimester and in the first 6 weeks post-partum. *What is Known Already:*

In vitro fertilization without pregnancy is not associated with increased venous thrombosis incidence. *Study Design, Size, Duration:* This national register-based cohort study covered the period from 1995 to 2005. *Participants/Materials, Setting, Methods:* All Danish pregnancies conceived by in vitro fertilization ( $n = 18,787$ ) were included. Venous thrombosis incidence rates in pregnancies after in vitro fertilization were compared with venous thrombosis incidence rates in reference pregnancies, by calculating incidence rate ratios. *Main Results and the Role of Chance:* In total, 48 cases were identified. In pregnancies after in vitro fertilization, the overall venous thrombosis incidence rate was 28.6 per 10,000 pregnancy-years (95% confidence interval (CI) 20.6–39.6) in comparison to 10.7 per 10,000 woman-years in reference pregnancies. Post-partum, the venous thrombosis incidence rate was 27.9 per 10,000 woman-years (95% CI 15.8–49.1) after in vitro fertilization in comparison to 17.5 per 10,000 woman-years in reference pregnancies. The overall venous thrombosis incidence rate ratio during in vitro fertilization (IVF) pregnancies compared with reference pregnancies was 3.0 (95% CI 2.1–4.3). The venous thrombosis incidence rate ratios during pregnancy were 2.8 (95% CI 1.9–4.1) in singleton IVF pregnancies and 4.4 (95% CI 2.4–8.3) in multiple IVF pregnancies, compared with reference pregnancies. The venous thrombosis incidence rate ratio post-partum was 1.2 (95% CI 0.6–2.8) for singleton IVF pregnancies and 3.9 (95% CI 1.7–8.8) for multiple IVF pregnancies compared with reference pregnancies. The post-partum venous thrombosis risk was higher in multiple IVF pregnancies compared with singleton IVF pregnancies. Maternal age, smoking and parity did not significantly affect the venous thrombosis risk. Ovarian hyperstimulation syndrome and polycystic ovarian syndrome did increase the risk of venous thrombosis during pregnancy. Caesarean section also increased the post-partum venous thromboembolism risk, but the increase was not significant. *Limitations, Reasons for Caution:* Other known confounders in our reference population could have contributed to the results. Access

to such data may have helped to explain the observations, but would not have changed the conclusion that IVF pregnancies have an increased risk of venous thrombosis compared with other pregnancies. *Wider Implications of the Findings*: Our study adds new insights by demonstrating an excess venous thrombosis incidence post-partum after in vitro fertilization. The high venous thrombosis incidence in first trimester after in vitro fertilization supports previous studies. Our findings are generalizable to other Western Countries. *Study Funding/Competing Interests*: Expenses for the acquirement of data were covered by a grant from The Secretary of Doctors further education, Central Denmark Region. None of the authors have any competing interests to declare.

**J.L. Serre et al., Does Anonymous Sperm Donation Increase the Risk for Unions between Relatives and the Incidence of Autosomal Recessive Diseases due to Consanguinity?**, *Hum Reprod* 29.3 (March 2014): 394–399 • In France gamete donation and notably sperm donation are anonymous. It has been claimed that anonymous artificial insemination by donor (AID) could highly contribute to an increase in the level of consanguinity and the incidence of autosomal recessive diseases, due to the unions between offspring of anonymous donors, unaware of their biological kinship, with the special case of unions between half-siblings. The actual incidence of consanguinity due to AID was compared with that resulting from the two other main sources of consanguinity and recessive diseases, i.e. voluntary unions between related individuals or inadvertent unions between the offspring of a common unknown male ancestor (false paternity). From these data, we estimated that expected unions in France between half sibs per year are 0.12 between offspring of sperm donors (1.2 every 10 years) and 0.5 between offspring of common male ancestors through false paternity (5 every 10 years). More generally, the inadvertent unions between false paternity offspring are roughly four times more frequent than those resulting from anonymous AID. We estimated that in the future, when AID has

been in practice for several generations, out the 820 000 annual births in France, respectively, 6 and 25 births will be consanguineous through an unknown common ancestor related to anonymous AID and to a false paternity, both of which are negligible when compared with the 1256 children born from first-degree cousins. About 672 children per year are born with a recessive genetic disease due to the panmictic risk and additional affected cases due to consanguinity would be 34.54 for first-cousin offspring, 0.33 for offspring of individuals related due to false paternity and 0.079 for offspring of individuals related due to anonymous AID. Anonymous AID would therefore be responsible for 0.46% of consanguineous births and for 0.01% of recessive diseases. Therefore, the effect of anonymous AID on half-sibling unions, consanguinity and recessive disease incidence can be regarded as marginal.

**R. Winand et al., In Vitro Screening of Embryos by Whole-Genome Sequencing: Now, in the Future or Never?**, *Hum Reprod* 29.4 (April 2014): 842–851 • *Study Question*: What are the analytical and clinical validity and the clinical utility of in vitro screening of embryos by whole-genome sequencing? *Summary Answer*: At present there are still many limitations in terms of analytical and clinical validity and utility and many ethical questions remain. *What Is Known Already*: Whole-genome sequencing of IVF/ICSI embryos is technically possible. Many loss-of-function mutations exist in the general population without serious effects on the phenotype of the individual. Moreover, annotations of genes and the reference genome are still not 100% correct. *Study Design, Size, Duration*: We used publicly available samples from the 1000 Genomes project and Complete Genomics, together with 42 samples from in-house research samples of parents from trios to investigate the presence of loss-of-function mutations in healthy individuals. *Participants/Materials, Setting, Methods*: In the samples, we looked for mutations in genes that are associated with a selection of severe Mendelian disorders with a known molecular basis. We looked for mutations

predicted to be damaging by PolyPhen and SIFT and for mutations annotated as disease causing in Human Genome Mutation Database (HGMD). *Main Results and the Role of Chance*: More than 40% of individuals who can be considered healthy have mutations that are predicted to be damaging in genes associated with severe Mendelian disorders or are annotated as disease causing. *Limitations, Reasons for Caution*: The analysis relies on current knowledge and databases are continuously updated to reflect our increasing knowledge about the genome. In the process of our analysis several updates were already made. *Wider Implications of the Findings*: At this moment it is not advisable to use whole-genome sequencing as a tool to set up health profiles to select embryos for transfer. We also raise some ethical questions that have to be addressed before this technology can be used for embryo selection.

### JAMA

*R. D. Adelman et al., Caregiver Burden: A Clinical Review, JAMA 311.10 (March 12, 2014): 1052–1060 • Importance*: Caregiver burden may result from providing care for patients with chronic illness. It can occur in any of the 43.5 million individuals providing support to midlife and older adults. Caregiver burden is frequently overlooked by clinicians. *Objectives*: To outline the epidemiology of caregiver burden; to provide strategies to diagnose, assess, and intervene for caregiver burden in clinical practice; and to evaluate evidence on interventions intended to avert or mitigate caregiver burden and related caregiver distress. *Evidence*: Cohort studies examining the relation between demographic and social risk factors and adverse outcomes of caregiver burden were reviewed. Review of recent meta-analyses to summarize the effectiveness of caregiver burden interventions were identified by searching Ovid MEDLINE, AgeLine, and the Cochrane Library. *Results*: Risk factors for caregiver burden include female sex, low educational attainment, residence with the care recipient, higher number of hours spent caregiving, depression, social isolation, financial stress, and lack of choice in

being a caregiver. Practical assessment strategies for caregiver burden exist to evaluate caregivers, their care recipients, and the care recipient's overall caregiving needs. A variety of psychosocial and pharmacological interventions have shown mild to modest efficacy in mitigating caregiver burden and associated manifestations of caregiver distress in high-quality meta-analyses. Psychosocial interventions include support groups or psychoeducational interventions for caregivers of dementia patients (effect size, 0.09–0.23). Pharmacologic interventions include use of anticholinergics or antipsychotic medications for dementia or dementia-related behaviors in the care recipient (effect size, 0.18–0.27). Many studies showed improvements in caregiver burden-associated symptoms (eg, mood, coping, self-efficacy) even when caregiver burden itself was minimally improved. *Conclusions and Relevance*: Physicians have a responsibility to recognize caregiver burden. Caregiver assessment and intervention should be tailored to the individual circumstances and contexts in which caregiver burden occurs.

*B. Gomes et al., Benefits and Costs of Home Palliative Care Compared With Usual Care for Patients with Advanced Illness and Their Family Caregivers, JAMA 311.10 (March 12, 2014): 1060–1061 • Clinical Question*: Are home palliative care services associated with benefits to patients with advanced illness and family caregivers, and are they cost-effective? *Bottom Line*: Compared with usual care, home palliative care is associated with increased odds of dying at home and fewer symptoms for patients with advanced illness. It is not associated with changes in caregiver grief. Cost-effectiveness is inconclusive.

### JAMA Internal Medicine

*T. N. Huynh et al., The Frequency and Cost of Treatment Perceived to Be Futile in Critical Care, JAMA Intern Med 173.20 (November 11, 2013): 1887–1894 • Importance*: Physicians often perceive as futile intensive care interventions that prolong life without achieving an effect that the patient can appreciate as a benefit. The prevalence

and cost of critical care perceived to be futile have not been prospectively quantified. *Objective:* To quantify the prevalence and cost of treatment perceived to be futile in adult critical care. *Design, Setting, and Participants:* To develop a common definition of futile care, we convened a focus group of clinicians who care for critically ill patients. On a daily basis for 3 months, we surveyed critical care specialists in 5 intensive care units (ICUs) at an academic health care system to identify patients whom the physicians believed were receiving futile treatment. Using a multivariate model, we identified patient and clinician characteristics associated with patients perceived to be receiving futile treatment. We estimated the total cost of futile treatment by summing the charges of each day of receiving perceived futile treatment and converting to costs. *Main Outcome and Measure:* Prevalence of patients perceived to be receiving futile treatment. *Results:* During a 3-month period, there were 6,916 assessments by 36 critical care specialists of 1136 patients. Of these patients, 904 (80%) were never perceived to be receiving futile treatment, 98 (8.6%) were perceived as receiving probably futile treatment, 123 (11%) were perceived as receiving futile treatment, and 11 (1%) were perceived as receiving futile treatment only on the day they transitioned to palliative care. The patients with futile treatment assessments received 464 days of treatment perceived to be futile in critical care (range, 1–58 days), accounting for 6.7% of all assessed patient days in the 5 ICUs studied. Eighty-four of the 123 patients perceived as receiving futile treatment died before hospital discharge and 20 within 6 months of ICU care (6-month mortality rate of 85%), with survivors remaining in severely compromised health states. The cost of futile treatment in critical care was estimated at \$2.6 million. *Conclusions and Relevance:* In 1 health system, treatment in critical care that is perceived to be futile is common and the cost is substantial.

*A. M. Torke et al., Scope and Outcomes of Surrogate Decision Making Among Hospitalized Older Adults, JAMA Intern Med 174.3 (March 1, 2014): 370–377 •*

*Importance:* Hospitalized older adults often lack decisional capacity, but outside of the intensive care unit and end-of-life care settings, little is known about the frequency of decision making by family members or other surrogates or its implications for hospital care. *Objective:* To describe the scope of surrogate decision making, the hospital course, and outcomes for older adults. *Design, Setting, and Participants:* Prospective, observational study conducted in medicine and medical intensive care unit services of 2 hospitals in 1 Midwestern city in 1,083 hospitalized older adults identified by their physicians as requiring major medical decisions. *Main Outcomes and Measures:* Clinical characteristics, hospital outcomes, nature of major medical decisions, and surrogate involvement. *Results:* According to physician reports, at 48 hours of hospitalization, 47.4% (95% CI, 44.4%–50.4%) of older adults required at least some surrogate involvement, including 23.0% (20.6%–25.6%) with all decisions made by a surrogate. Among patients who required a surrogate for at least 1 decision within 48 hours, 57.2% required decisions about life-sustaining care (mostly addressing code status), 48.6% about procedures and operations, and 46.9% about discharge planning. Patients who needed a surrogate experienced a more complex hospital course with greater use of ventilators (2.5% of patients who made decisions and 13.2% of patients who required any surrogate decisions;  $P < 0.001$ ), artificial nutrition (1.7% of patients and 14.4% of surrogates;  $P < 0.001$ ), and length of stay (median, 6 days for patients and 7 days for surrogates;  $P < 0.001$ ). They were more likely to be discharged to an extended-care facility (21.2% with patient decisions and 40.9% with surrogate decisions;  $P < 0.001$ ) and had higher hospital mortality (0.0% patients and 5.9% surrogates;  $P < 0.001$ ). Most surrogates were daughters (58.9%), sons (25.0%), or spouses (20.6%). Overall, only 7.4% had a living will and 25.0% had a health care representative document in the medical record. *Conclusions and Relevance:* Surrogate decision making occurs for nearly half of hospitalized older

adults and includes both complete decision making by the surrogate and joint decision making by the patient and surrogate. Surrogates commonly face a broad range of decisions in the intensive care unit and the hospital ward setting. Hospital functions should be redesigned to account for the large and growing role of surrogates, supporting them as they make health care decisions.

### Journal of the American Geriatrics Society

**C. T. Su et al., Family Matters: Effects of Birth Order, Culture, and Family Dynamics on Surrogate Decision-Making, *J Am Geriatr Soc* 62.1 (January 2, 2014): 175–182 •** Cultural attitudes about medical decision-making and filial expectations may lead some surrogates to experience stress and family conflict. Thirteen focus groups with racially and ethnically diverse English and Spanish speakers from county and Veterans Affairs hospitals, senior centers, and cancer support groups were conducted to describe participants' experiences making serious or end-of-life decisions for others. Filial expectations and family dynamics related to birth order and surrogate decision-making were explored using qualitative, thematic content analysis, and overarching themes from focus group transcripts were identified. The mean age of the 69 participants was  $69 \pm 14$ , and 29% were African American, 26% were white, 26% were Asian or Pacific Islander, and 19% were Latino. Seventy percent of participants engaged in unprompted discussions about birth order and family dynamics. Six subthemes were identified within three overarching categories: communication (unspoken expectations and discussion of death as taboo), emotion (emotional stress and feelings of loneliness), and conflict (family conflict and potential solutions to prevent conflict). These findings suggest that birth order and family dynamics can have profound effects on surrogate stress and coping. Clinicians should be aware of potential unspoken filial expectations

for firstborns and help facilitate communication between the patient, surrogate, and extended family to reduce stress and conflict.

### Obstetrics and Gynecology

**R. Peragallo Urrutia et al., Risk of Acute Thromboembolic Events With Oral Contraceptive Use: A Systematic Review and Meta-analysis, *Obstet Gynecol* 122.2 (August 2013): 380–389 •** *Objective:* To estimate the risk of venous thromboembolism, stroke, or myocardial infarction (MI) associated with the use of oral contraceptive pills (OCPs) and to describe how these risks vary by dose or formulation. *Data Sources:* We searched PubMed, Embase, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov for studies published from January 1995 through June 2012 that evaluated the association between OCP use and risk of venous thromboembolism, stroke, or MI. *Method of Study Selection:* We reviewed 6,476 citations. We included English-language, controlled studies with human participants reporting a quantitative association between exposure to OCPs and outcomes of venous thromboembolism, stroke, or MI. Two investigators independently reviewed articles for inclusion or exclusion; discordant decisions were resolved by team review and consensus. Random-effects meta-analysis was used to generate summary odds ratios (ORs). *Tabulation, Integration, and Results:* Fifty studies met inclusion criteria. There were no randomized clinical trials. We found threefold increased odds of venous thromboembolism among current compared with noncurrent OCP users (14 studies; OR 2.97, 95% confidence interval [CI] 2.46–3.59). We found twofold increased odds of ischemic stroke (seven studies; OR 1.90, 95% CI 1.24–2.91). There was no evidence of increased risk of hemorrhagic stroke (four studies; OR 1.03, 95% CI 0.71–1.49) or MI (eight studies; OR 1.34, 95% CI 0.87–2.08). *Conclusion:* Current use of combined OCPs is associated with increased odds of venous thromboembolism and ischemic stroke but not hemorrhagic stroke or MI.