stable. Tissue immediately next to the fibroed alginate implant also showed an increased expression of the macrophage marker CD68 and the local inflammation marker TGFβ1 together with a delayed increase in the B cell marker CD19.

Removal of innate immune macrophages by clodosome treatment eliminated the fibrosis of hydrogel alginate. However, clodosome treatment also eliminated the innate immune population entirely, thus limiting its clinical application. Inhibition of cytokine receptor colony stimulating factor-1 receptor, however, reduced host immune-mediated recognition and propagation of foreign body rejection while preserving essential macrophage functions.

These findings provide not only insights into the immunological basis of foreign body responses but may also provide the basis for the development of macrophage-specific agents that may be integrated into drug-elution systems reducing the fibrotic response to implanted medical devices.

**Single-Cell RNA-Seq Reveals New Types of Human Blood Dendritic Cells, Monocytes, and Progenitors**

Villani AC, Satija R, Reynolds G, et al. Science. 2017;356(6335).

Dendritic cells (DCs) and monocytes (MCs) play a central role in pathogen sensing, phagocytosis and antigen presentation and consist of multiple specialized subtypes, which regulate innate and adaptive immune responses. DCs and MCs are defined according to a combination of molecular markers, functional properties and ontogeny with a simple classification of plasmacytoid DCs or as one of 2 types of conventional DC populations. The authors addressed the limitations of the existing classification of DCs.

To determine the subtypes of DCs and MCs in human blood, the authors developed an experimental and computational approach performing single-cell RNA sequencing on DCs and MCs derived from a single healthy individual identifying subsequently clusters of cells that are similar to each other. Discriminative surface markers were defined per cluster and then used to prospectively isolate cells corresponding to these key clusters. Comprehensive profiling of gene expression at single-cell resolution was used to validate the identity of the cell subtypes. This method was repeated in 10 individuals resulting in 2400 cells. Lastly, the authors performed a functional analysis for selected cell types. Those efforts resulted into a more accurate taxonomy that includes 6 DC subclasses, 4 MC subclasses with 1 conventional DC progenitor presented in this study.

Using discriminative markers associated with the newly defined DC subtypes, the authors assessed the functions of some of these DC subtypes. The study reveals a new DC subset that shares properties with plasmacytoid DCs and potentially activates T cells.

This study has several implications. The discovery of several DC subsets will enable a more in-depth understanding of the role and function of DCs in tissues, inflammation, and disease. The identification of circulating CD100hiCD34int progenitors provides a well-defined cell type for generating DCs in vitro and for therapeutic targeting. The use of this new DC atlas illustrates how single-cell analysis can pinpoint relationships of diseased cells to healthy cells.

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**eResources**

**Contraception for Transplant Patients**

Andrea H. Roe, MD, MPH and Caryn Dutton, MD, MS

This eResources article provides links to patient education materials that can aid in the selection of a contraceptive method and links to medical guidelines that can help healthcare providers evaluate the safety of specific methods in women with complex medical conditions.

**BACKGROUND**

Forty percent of all pregnancies worldwide are unintended (either unplanned or mistimed). For women with preexisting medical conditions, unintended pregnancy may worsen their disease, be associated with poor pregnancy outcomes, expose the pregnancy to potentially teratogenic medicines, or render patients ineligible for interventions such as organ transplant. Unfortunately, women who may have increased medical and obstetrical risk in pregnancy have the same rates of unintended pregnancy as the general population.
Most female transplant patients are sexually active, and ovulation and menstruation (although sometimes irregular) usually resume within months after transplant surgery. The unintended pregnancy rate among transplant patients has been reported as high as 93% and the rate of contraceptive use only 48% to 72%. To reduce the risks of unintended pregnancy and to address the unmet need for contraception, contraception must be incorporated into the clinical care of transplant patients.

CONTRACEPTIVE METHODS

Modern contraceptive methods vary in their reversibility, mode of delivery, length of use, hormonal composition, and effectiveness at preventing pregnancy. The World Health Organization and the United States Centers for Disease Control and Prevention provide a patient guide to contraceptive methods listed in tiers according to their effectiveness [A]. Fact sheets are available to educate patients about contraceptive options [B, C], some of which are in Spanish, Chinese, and Portuguese, in addition to English [C]. The Bedsider Web site has an interactive contraception guide that includes photos and video testimonials [D].

Current methods of contraception are briefly described here:

- **Permanent sterilization** includes vasectomy, tubal sterilization, and hysterectomy surgical occlusion, which are highly effective surgical procedures that are irreversible and appropriate only for patients who are certain that they do not desire or have completed childbearing.

- **Long-acting reversible contraception** is as effective as sterilization but is not permanent. These are small devices that are inserted in the uterus or subdermally in the arm and can remain in place for up to several years. The copper intrauterine device (IUD) is hormone-free, whereas the hormonal IUDs and implants deliver a progestin.

- **Progestin injections** are used monthly or every 3 months and are highly effective.

- **Combined hormonal contraception** includes a daily oral pill, long-acting reversible contraception or injections, primarily hormone delivery via a daily patch, and monthly vaginal ring, all of which deliver both an estrogen and a progestin. The estrogen component increases risk for venous and arterial thrombosis, especially in women with underlying risk factors. Compared with older formulations, modern versions of the pill contain lower doses of estrogen and therefore carry a lower thrombogenic risk. These methods are less effective than long-acting reversible contraception or injections, primarily because of patient nonadherence.

- **Progestin-only pills** require daily administration and do not contain estrogen.

- **Emergency contraception** is a pill that may be used within several days of unprotected intercourse to delay ovulation and prevent pregnancy. This Web site can help patients navigate access to emergency contraception [E].

- **Barrier contraception** includes condoms, diaphragms, cervical caps, and spermicide. These methods are used with each episode of coitus and contain no hormones. These are the least effective of the methods presented here; with typical use, 12% to 21% of women relying on these methods will become pregnant within 1 year.

CONTRACEPTIVE SAFETY IN TRANSPLANT PATIENTS

The World Health Organization publishes evidence-based and consensus guidelines evaluating the relative safety of contraception in women with specific medical conditions (Medical Eligibility Criteria for Contraceptive Use) [F]. Similar guidelines have been adapted and issued in the United States and the United Kingdom [G, H]. A single-page summary chart is also available for easy reference [I]. For each medical condition, contraceptive methods are classified as follows: Category 1: No restriction Category 2: Advantages generally outweigh theoretical or proven risks Category 3: Theoretical or proven risks generally outweigh the advantages

The US Centers for Disease Control and the UK Medical Eligibility Criteria for Contraceptive Use state that women with uncomplicated solid organ transplants may initiate any method of contraception (barrier methods are category 1, and all nonbarrier methods are category 2). Women with complicated solid organ transplants, defined as acute or chronic graft failure, rejection, or cardiac allograft vasculopathy, may safely initiate the progestin implant, progestin injection, and progestin pills (category 2) and may continue to use IUDs that are already in place (category 2). For complicated transplant patients, inserting a new IUD is not advisable (category 3). Combined hormonal contraception is contraindicated for both women with complicated solid organ transplants and women with Budd-Chiari syndrome (category 4).

Clinical studies of contraception in transplant patients are limited in both number and size. In small prospective studies, renal and liver transplant patients using the combined hormonal pill, patch, and ring for more than 12 months did not become pregnant and maintained stable transplant function [9, 10]. In one of these studies, antihypertensive regimens did require adjustment in some patients, and 2 patients discontinued the pill because of lower extremity thromboembolism and acute graft rejection [9].

Historical concern about IUD use after transplantation stems from case reports of contraceptive failure and bacterial peritonitis in renal transplant patients thought to be linked to chronic immunosuppression [11]. However, more recent case series of transplant patients using IUDs demonstrated contraceptive efficacy and safety, with no unintended pregnancies or pelvic infections [12, 13]. Serum and intrauterine biomarkers measured before and after progestin IUD insertion provide evidence of a local, but not systemic, inflammatory response in both transplant patients and healthy controls [14]. Furthermore, more robust clinical literature of HIV patients has shown that the copper IUD is both safe and effective in this immunosuppressed population [15].

When choosing appropriate contraception with a transplant patient, comorbidities and medications must be considered along with the patient’s clinical status. For example, certain medical conditions, such as uncontrolled hypertension or a history of venous thromboembolism, preclude use of exogenous estrogen, and immunosuppressive therapies may affect or be affected by contraceptive hormone metabolism.

GENERAL APPROACH TO CONTRACEPTION FOR THE TRANSPLANT PATIENT

For the transplant provider, it is important to address contraception with reproductive-age patients at the pretransplant evaluation, because women must delay pregnancy until at least 1 year after transplant, and at follow-up visits [16]. This
topic can be introduced with a simple question: “Would you like to become pregnant in the next year?” (This is branded as One Key Question [J], a campaign to encourage physicians to routinely screen patients for contraceptive need.) Depending on the patient’s response, she may be referred to a gynecologist or family planning specialist for contraception counseling and provision or to an obstetrics specialist for pregnancy planning and management. Women needing contraception should be encouraged to use barrier methods as a bridge to more effective contraception.

Coordination of reproductive care between transplant teams and obstetrician/gynecologists minimizes the unnecessary morbidity of unintended pregnancy and optimizes the safety of intended pregnancy among transplant patients.

**Links**

For patients:

[A] https://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf

[B] http://www.arhp.org/publications-and-resources/patient-resources/fact-sheets

[C] http://www.reproductiveaccess.org/key-areas/contraception/

[D] https://www.bedsider.org/methods

[E] http://ec.princeton.edu/providers/index.html

For providers:

[F] http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/

[G] https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6503.pdf

[H] https://www.fsrh.org/standards-and-guidance/external/ukmec-2016-digital-version/

[I] https://www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf

[J] http://www.onekeyquestion.org

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