Contraception 100 (2019) 26–30

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/con

Original research article

Neurovascular anatomy of the adult female medial arm in relationship to potential sites for insertion of the etonogestrel contraceptive implant☆,☆☆,★

Joe Iwanaga [a], Michelle C. Fox [b,*], Hans Rekers [b], Lisa Schwartz [b], R. Shane Tubbs [a]

[a] Seattle Science Foundation, Seattle, WA
[b] Merck & Co., Inc., Kenilworth, NJ, USA

ARTICLE INFO

Article history:
Received 19 October 2018
Received in revised form 20 February 2019
Accepted 20 February 2019

Keywords:
Neurovascular anatomy
Contraceptive implant
Etonogestrel implant
Nerve injury

ABSTRACT

Objective: Anatomic assessment of the medial upper arm to identify potential sites for insertion of the etonogestrel (ENG) implant.
Study design: Forty female cadaveric arms were dissected. Two rows of 1×2-cm dissection windows were created in the inner arm overlying the triceps approximately 2–3 and 4–5 cm posterior to the bicipital sulcus (sulcus). The primary window was 8–10 cm proximal to the medial epicondyle and approximately 2–3 cm posterior to the sulcus. Neurovascular structures within each window were identified. The entire medial upper arm was dissected to visualize underlying structures.
Results: Mean age (± SD) of cadavers at death was 72.0±11.0 years. Arm measurements at the primary window were circumference 28.2±4.8 cm [range: 21–41], skin thickness 0.6±0.2 mm [0.3–1.0] and subcutaneous tissue thickness: 12.3±4.9 mm [4.7–21]. The basilic vein and the medial brachial cutaneous, ulnar and medial antebrachial cutaneous nerves were located in 40%, 58%, 40% and 18% of the primary windows, respectively. No major neurovascular structures were located 3–5 cm posterior to the sulcus. More neurovascular structures were identified overlying the biceps than triceps. Elbow flexion with the hand underneath the head displaced the ulnar nerve anteriorly towards the sulcus.
Conclusion: As no major neurovascular structures were identified overlying the triceps 8–10 cm proximal to the medial epicondyle and 3–5 cm posterior to the sulcus, ENG implant insertion at this location may minimize risk of injury associated with improper deep insertion. Elbow flexion deflects the ulnar nerve away from this area and may further decrease risk of injury secondary to inadvertent deep insertion.
Implications: Although a limited cadaver study, this anatomic assessment provides rationale for insertion of the ENG implant overlying the triceps 8–10 cm proximal to the medial epicondyle and 3–5 cm posterior to the sulcus. This area is theoretically safer for insertion of the ENG implant than areas of the inner arm where major neurovascular structures are commonly located.

1. Introduction

Contraceptive implants provide highly reliable, rapidly reversible long-term prevention of pregnancy. Two types of implants are marketed globally [1–3]; availability varies by country. The etonogestrel (ENG) implant is a single rod measuring 4 cm long and 2 mm in diameter [1]. The levonorgestrel implant contains two rods, each slightly larger than the ENG implant [2,3]. Since approval of the first devices in the 1980s, contraceptive implants have been placed subdermally in the upper medial arm.

Within the medial arm, several prominent neurovascular structures are present including the brachial artery, the cephalic and basilic veins and the median, medial brachial cutaneous, medial antebrachial cutaneous and ulnar nerves. Contraceptive implants should be placed just

☆ Funding: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.
☆☆ Conflicts of interest: Michelle C. Fox, Hans Rekers and Lisa Schwartz are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may hold stock/stock options in the company which is the Marketing Authorization Holder of the etonogestrel contraceptive implant. Joe Iwanaga has received a stipend for completing the cadaver dissections. R. Shane Tubbs has received reimbursement for supplies and travel as well as honoraria.
★ Disclosures: Joe Iwanaga, Michelle C. Fox, Hans Rekers, Lisa Schwartz and R. Shane Tubbs are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, and interpretation of data, in addition to drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
* Corresponding author. Tel.: +1 732 594 2312.
E-mail address: michelle.fox2@merck.com (M.C. Fox).

https://doi.org/10.1016/j.contraception.2019.02.007
0010-7824/

under the skin. Incorrect procedural technique may result in deep insertion, making the implant difficult to palpate or remove. Deep implant insertion or efforts to remove a deeply placed implant adjacent to major vessels or nerves may result in rare cases of neurovascular injury (e.g., nerve damage or hematoma) [1–8]. As noted in case reports, implant placement on or near a nerve may be associated with paresthesia or pain [4,6]. Ulnar nerve injury may also occur during insertion or removal if the implant is placed too close to the elbow, where the nerve travels superficially. Nerve injuries, albeit rare, may result in permanent sensorimotor dysfunction or chronic neuropraxia if not diagnosed and repaired [4,7,8]. Furthermore, improper deep placement may result in rare intravascular insertion and possible implant migration to the pulmonary artery [9]. Placement in a region free from underlying major neurovascular structures is expected to decrease risk of potential injury during insertion or removal of the implant.

The ENG and levonorgestrel implants instructions differ regarding insertion site location. Labels specify distance from the elbow (e.g., 8–10 cm proximal to the medial epicondyle) to ensure that the implant is not placed closer to the elbow where the ulnar nerve is superficial and more prone to injury [1–3]. Initially, implants were placed over the bicipital sulcus (sulcus); however, later ENG implant instructions advised that this area overlies prominent vessels and nerves and should be avoided [1].

Figures within ENG implant instructions have shown the implant located overlying the triceps away from the sulcus; however, in 2016, the United Kingdom Faculty of Sexual and Reproductive Healthcare recommended placement overlying the biceps, favoring this location to avoid the path of the ulnar nerve [10]. In 2017, due to debate among experts in implant use, the Marketing Authorization Holder (MAH) for the ENG implant (Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) organized a consultants meeting to obtain input on anatomical considerations, clinical experience and expert opinion regarding implant insertion site location. The attendees, which included reproductive health clinical experts and specialists in arm surgery and anatomy, unanimously concluded that placement over the triceps is preferred given more significant neurovascular structures overlying the biceps. They recommended further assessment of the anatomy of the inner arm to potentially identify more precisely the site(s) overlying the triceps free from major neurovascular structures at risk for potential injury. Subsequently, the MAH for the ENG implant funded an independent anatomic assessment performed at the Seattle Science Foundation. This publication describes the anatomic findings in relation to potential sites for insertion of the ENG implant.

2. Methods

2.1. Study details

Two clinical anatomists (J.I. and R.S.T.) performed dissections of 40 arms from 20 fresh frozen female cadavers. The work was performed in accordance with the requirements of the Declaration of Helsinki. When necessary, the anatomists performed dissections under a surgical microscope (OPMI CS NC31, Carl Zeiss, Oberkochen, Germany).

Prior to dissection, the anatomists measured the length of each arm and forearm (Supplemental Fig. 1). Next, with each specimen supine, the arm was abducted approximately 90° and the elbow flexed. All dissections and photographs were performed with the hand placed under the head (Fig. 1). All structures were examined with the elbow at 90° and 180° (i.e., fully extended).

The anatomists marked lines on the skin from the midpoint of the medial epicondyle to a point 8–10 cm proximally along the junction between the anterior and posterior compartments of the arm [i.e., the sulcus (groove) between the brachialis/biceps anteriorly and triceps posteriorly]. Hereafter, this line is referred to as the *sulcal line* (Fig. 2A). The primary dissection window (hereafter named the *primary window*) approximately 1×2 cm was created with a scalpel approximately 2–3 cm posterior to the sulcal line and 8–10 cm proximal to the medial epicondyle. The circumference of the arm was measured at the primary window, 8–10 cm proximal to the medial epicondyle. As shown in Fig. 2B, the anatomists dissected additional windows parallel to the primary window approximately 2–3 cm posterior to the sulcal line at one third and two thirds of its length. Dissection was performed into the subcutaneous tissues and deep fascia to examine the neurovascular contents in each window. Each anatomist measured the thickness of the skin and subcutaneous tissues using microcalipers (Mitutoyo, Kanagawa, Japan) with a resolution of 0.01 mm and accuracy of ±0.025 mm. Both anatomists performed tissue thickness measurements in triplicate on all specimens, and results were averaged. Sequential dissection of each tissue layer is shown in Supplemental Fig. 2.

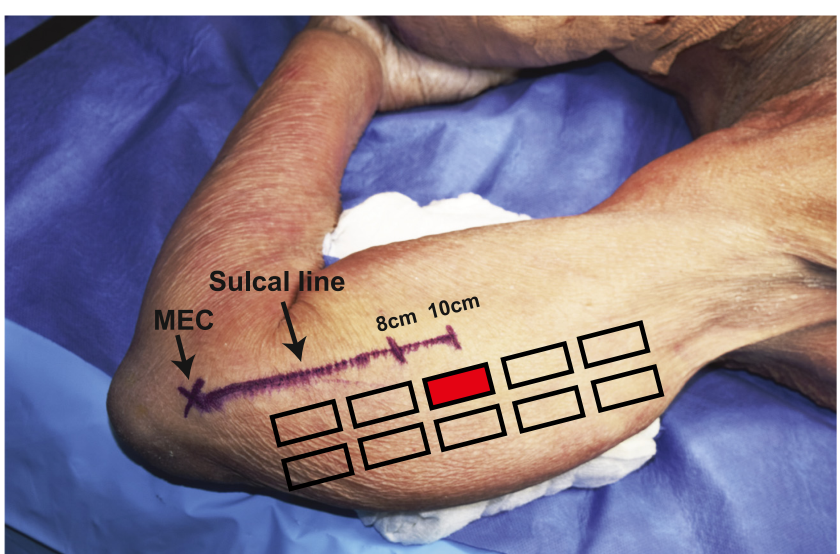

Fig. 1. Right upper limb illustrating the positioning of the cadavers for dissection. The medial epicondyle (MEC) is marked with an "X." Vertical marks are drawn at 8 and 10 cm from the MEC on the sulcal line. Two rows of dissection windows are displayed with the primary window (8-10 cm from the MEC and approximately 2-3 cm posterior to the sulcus) shaded red.

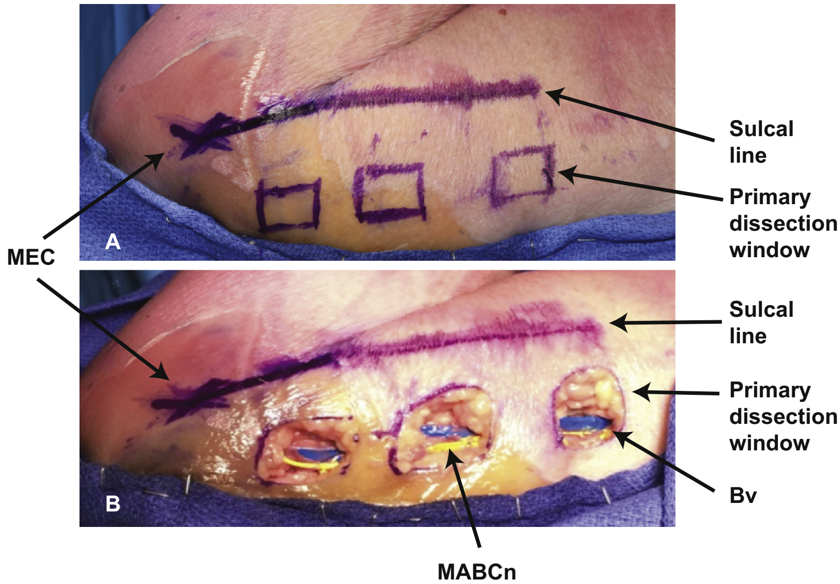

Fig. 2. Right medial arm. (A) Sulcal line and dissection windows located approximately 2–3 cm posterior to the sulcal line. The primary dissection window [at 8–10 cm proximal to the medial epicondyle (MEC)] is furthest to the right. Secondary windows at one third and two thirds of the length of the sulcal line. (B). Dissection performed demonstrating the basilic vein (Bv, which is colored blue) and the medial antebrachial cutaneous nerve (MABCn, which is colored yellow). Note that the same anatomical contents are seen throughout the row of windows.

Similar 1×2-cm windows were made approximately 4–5 cm posterior to the sulcal line, and the above process was repeated (Fig. 3). Dissection windows were similarly created proximally towards the axilla (Supplemental Fig. 3). The anatomists confirmed the identity of each structure within a window by further dissection proximally and distally. Once anatomical structures were identified, their movement was assessed during flexion and extension of the elbow (Supplemental Video).

Lastly, the entire medial arm was dissected from the axilla to the elbow to visualize all neurovascular structures and their positions relative to the sulcal line proximal and distal to the dissection windows (Supplemental Fig. 4). This also allowed observation of the course of all major neurovascular structures anterior to the sulcal line overlying the biceps.

2.2. Data analysis

Sample size was chosen for feasibility. Measurements were averaged and presented using descriptive statistics. We summarized the number of major neurovascular structures (medial brachial cutaneous nerve, ulnar nerve, basilic vein and medial antebrachial cutaneous nerve) detected in the primary window as a score from 0 (i.e., no major structures present) to 4 (i.e., all structures present). Statistical testing was performed using t tests to assess for differences in measurements and total number of major neurovascular structures between the right and left arms with a p value <.05 considered significant.

Table 1
Arm measurements

Measurement	Range	Mean ± SD
Length of arm, cm	28–35	31.1±1.6
Length of forearm, cm	40–49	44.4±2.3
Length of upper limb (arm + forearm), cm	70–81	75.5±3.1
Angle of elbow in flexion, °	10–34	19.7±5.8
Circumference of upper arm, cm	21–41	28.2±4.8
Skin thickness, mm	0.33–1.0	0.6±0.2
Subcutaneous tissue thickness, mm	4.7–21.0	12.3±4.9

Arm length is defined as the distance between the acromion and medial epicondyle. Forearm length is defined as the distance from the medial epicondyle to tip of the third digit. The length of the upper limb is the sum of the arm and forearm lengths.

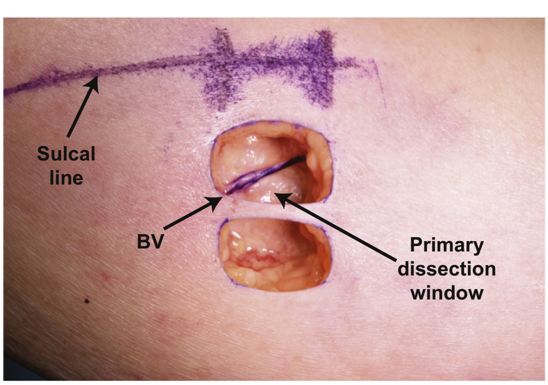

Fig. 3. Right medial arm showing location of primary dissection window approximately 2–3 cm posterior to the sulcal line. The primary window contains the basilic vein (Bv) and the more posterior window shows only the deeper triceps muscle with no major overlying neurovascular structures.

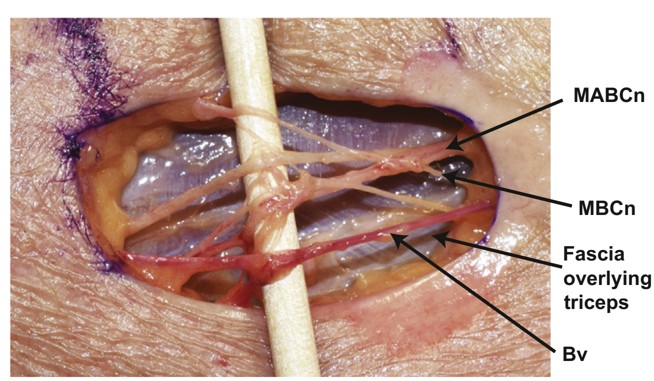

Fig. 4. Dissection demonstrating the superficial nerves including the medial antebrachial cutaneous nerve (MABCn) and the medial brachial cutaneous nerve (MBCn), located with the subcutaneous tissue within the primary window overlying the triceps muscle. The basilic vein (Bv) is also identified.

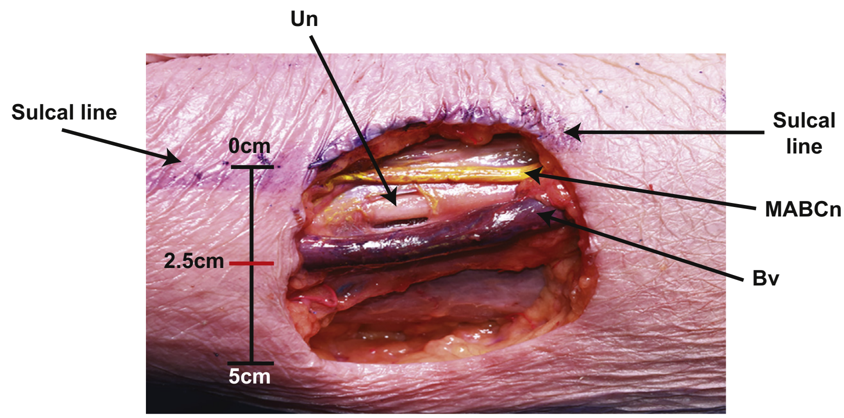

Fig. 5. Right cadaveric arm showing from top to bottom, the medial antebrachial cutaneous nerve (MABCn), ulnar nerve (Un) and the basilic vein (Bv) within the primary dissection window. The Un is beneath the fascia overlying the triceps and is exposed by removing a segment of the deep fascia. Note the absence of neurovascular structures more posteriorly (i.e., 3–5 cm posterior to the sulcus).

3. Results

Nineteen Caucasian and one Hispanic cadavers were dissected. Age at death ranged from 55 to 90 years (mean ± SD: 72.0±11.0 years). Arm measurements are summarized in Table 1. Arm circumference at the primary window ranged from 21 to 41 cm. No specimen had signs of trauma, pathology or prior surgery in any dissected areas. There were no significant differences between measurements obtained from the right and left arms of each cadaver (data not shown).

The general anatomy of the inner arm encountered during dissection is described below. In the superficial anterior compartment (overlying the biceps), several prominent neurovascular structures were detected including the brachial artery and vein, median nerve, musculocutaneous nerve, and the cephalic vein and its tributaries (Supplemental Fig. 4). In the subcutaneous tissues superficial to the deep fascia covering the triceps, the medial antebrachial cutaneous nerve travels anteriorly to ulnar nerve, and the medial brachial cutaneous nerve travels posteriorly along the course of the basilic vein (Supplemental Fig. 5). Multiple branches of superficial nerves (medial antebrachial cutaneous nerve, medial brachial cutaneous nerve) were located within the primary window (Fig. 4). In all specimens, the ulnar nerve was located underneath the fascia covering the triceps muscle 8–10 cm proximal to the medial epicondyle (Fig. 5). The ulnar nerve pierces this fascia and becomes superficial 6–8 cm proximal to the medial epicondyle.

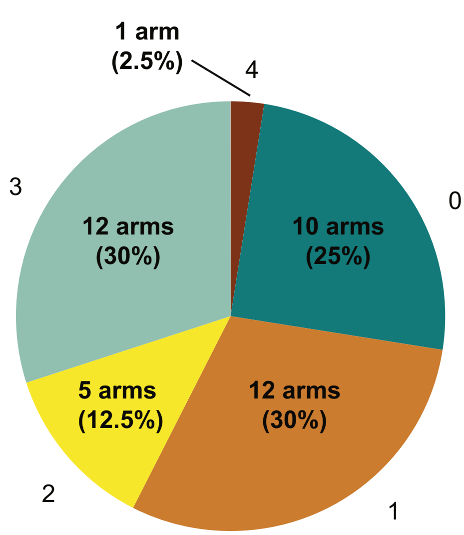

Fig. 6. Number of neurovascular structures [total count (0–4) of ulnar nerve, basilic vein, medial antebrachial cutaneous nerve and medial brachial cutaneous nerve)] in the primary window (8–10 cm proximal to the medial epicondyle and approximately 2–3 cm posterior to the sulcus).

Fig. 6 demonstrates the distribution of the total number (range 0–4) of major neurovascular structures contained with the primary window of each specimen. Only 25% of the primary windows were free of major neurovascular structures. The medial brachial cutaneous nerve, ulnar nerve, basilic vein and medial antebrachial cutaneous nerve were identified in the primary window in 23 (57.5%), 16 (40.0%), 16 (40.0%) and 7 (17.5%) arms, respectively. A similar presence of neurovascular structures was demonstrated in the row of windows dissected approximately 2–3 cm posterior to the sulcal line proximally and distally to the primary window; however, the ulnar nerve was slightly more posterior closer to the axilla. None of the four major neurovascular structures were detected 3 to 5 cm posterior to the sulcal line. With elbow flexion, the ulnar nerve moves anteriorly towards the sulcus. The Supplemental Video (available online) shows the movement of the ulnar nerve with flexion/ extension of the elbow. Neither flexion nor extension affected the position of the other identified vessels and nerves.

4. Discussion

This is the first investigation of potential sites for contraceptive implant insertion using cadaver dissection. We demonstrate the variability in anatomy in terms of location of major neurovascular structures within and surrounding the sulcus. We found that major vessels and nerves were not usually confined to the sulcus. The region 2–3 cm posterior to the sulcus was free from major neurovascular structures in only one fourth of specimens, suggesting that implant placement in this area may still carry risk of potential injury in case of inadvertent deep insertion.

We did not identify any major neurovascular structures in the midportion of the inner upper arm overlying the triceps 3–5 cm posterior to the sulcus and at least 8 cm proximal to the medial epicondyle. This area theoretically carries the least risk of neurovascular injury or intravascular insertion. Although the exact site of implant insertion is less important than assuring a superficial placement (to facilitate localization and removal and avoid injury to deep structures), placement in a region free of major neurovascular structures further mitigates risks in the event of incorrect deep insertion.

The dissections performed during this study confirmed that the vessels and nerves overlying the biceps are larger and more prominent than those over the triceps and are thus presumably more at risk to neurovascular injury (i.e., median nerve) and intravascular insertion (i.e., cephalic vein). Proponents of inserting contraceptive implants overlying the biceps cite concern for potential ulnar nerve injury [10].

However, the ulnar nerve is unlikely to be injured when the implant insertion site is located 8–10 cm proximal to the medial epicondyle and 3–5 cm posterior to the sulcus, as the ulnar nerve is not located at that site. Our findings suggest that the ulnar nerve may be further protected during insertion and removal of implants overlying the triceps by flexing the elbow with the hand positioned under the head to deflect the nerve anteriorly.

This anatomic assessment has several limitations. First, this was not a clinical study involving implant insertion in live young women; thus, the potential impact on clinical safety is implied. Contraceptive implants were not placed during dissections to confirm absence of neurovascular injury; we considered this unnecessary in the absence of major structures at the recommended insertion site in all specimens. These cadaveric specimens were from women older than contraceptive implant users. While anatomic differences from younger women cannot be excluded, the neurovascular anatomy of the arm is not known to change with age. Though the body mass index (BMI) of the cadavers is unknown, middle upper arm circumference approximates BMI and may be used to assess nutritional status; adult middle arm circumference <23 cm usually indicates being underweight and values >32 cm indicate obesity [11–13]. Though the circumference measured at the primary window may slightly differ from the standard measurement through the midpoint of the upper arm, the wide range in measurements in this study (i.e., 21–41 cm) indicates that both underweight and obese specimens were examined and that the findings were independent of arm size. The cadavers were racially and ethnically similar (mostly Caucasian non-Hispanic); thus, the assessment may not apply to all users of the implant. A larger sample with a greater diversity in specimens might provide additional information regarding anatomic variation. We limited this assessment to the medial upper arm, the conventional insertion site for contraceptive implants, and did not explore alternative locations.

As shown in published case reports, neurovascular injuries are usually associated with user errors including deep insertion, insertion too close to the elbow or blind dissection deep within the arm during attempted removal [4–8]. While nerve injury associated with insertion or removal of the contraceptive implant is rare, the sequelae can result in permanent pain or sensorimotor loss if the injury is not repaired. As suggested by the results of this anatomic assessment, small adjustments to the insertion site and arm positioning may be useful to further reduce this potential risk by moving instrumentation to a region most likely to be free of underlying major neurovascular structures.

Healthcare professionals inserting and removing contraceptive implants should be aware of the ways to avoid potential injury to major neurovascular structures by assuring a superficial insertion of the implant and avoiding placement near major neurovascular structures. To minimize risk, removal of deeply placed implants or those known to be near vessels and nerves should be performed by those familiar with arm anatomy and the techniques needed to localize and remove implants from these locations [1,14]. Furthermore, to prevent potential injury from blind exploration or deep dissection within the arm, a nonpalpable implant should be localized with imaging before removal attempts to understand its proximity to surrounding neurovascular structures [1,8,14].

To avoid injury to underlying neurovascular structures, implants should be placed superficially. Placement in a region free of major underlying neurovascular structures reduces the potential for injury in the event of improper deep insertion. Based on the findings from this anatomic assessment, which demonstrated a region free of major neurovascular structures in all 40 dissections, the MAH for the ENG implant revised the insertion instructions for the ENG implant to specify the insertion site to be 3–5 cm posterior to the sulcus and 8–10 cm proximal to the medial epicondyle. As very thin women may have small arms such that insertion 3–5 cm posterior to the sulcus may place the implant on the back of the arm rather than medially, the MAH for the ENG implant revised the label to advise placement "as far posterior from the sulcus as possible" in this situation such that the implant remains in the more discreet region of the inner arm. Additionally, the MAH for the ENG implant recommends elbow flexion with the hand under the head during insertion/removal for all patients as this will anteriorly displace the ulnar nerve away from the recommended insertion site and potentially further decrease chance of injury. These changes were made within the United States Prescribing Information in the fall of 2018 and are accessible online [1]; updates to product labeling may be under regulatory review in other countries. Further information may be obtained by contacting the local MAH for the ENG implant.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.02.007.

Acknowledgments

Medical writing and editorial assistance provided by Alan Meehan and Jennifer Rotonda of Merck & Co., Inc., Kenilworth, NJ, USA.

References

[1] Nexplanon (etonogestrel implant) prescribing information (revised: October 2018). Merck & Co., Inc., Whitehouse Station, NJhttps://www.merck.com/product/usa/pi_circulars/n/nexplanon/nexplanon_pi.pdf. [Last accessed October 15, 2018].
[2] Jadelle sine inserter SmPC prescribing Information (revised: Dec 2016). Bayer Healthcare, Finlandhttps://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020544s010lbl.pdf. [Last accessed August 22, 2018].
[3] Levoplant overview and use (revised: July 2018). Shanghai Dahua Pharmaceutical Co., LTD, Chinahttps://www.fhi360.org/sites/default/files/media/documents/resource-sino-levoplant-english.pdf. [Last accessed August 22, 2018].
[4] Laumonerie P, Blasco L, Tibbo ME, Leclair O, Kerezoudis P, Chantalat E, et al. Peripheral nerve injury associated with a subdermal contraceptive implant: illustrative cases and systematic review of literature. World Neurosurg 2018;111:317–25.
[5] Smith JW, Conwit RA, Blumenthal PD. Ulnar nerve injury associated with removal of Norplant implants. Contraception 1998;57(2):99–101.
[6] Brown M, Britton J. Neuropathy associated with etonogestrel implant insertion. Contraception 2012;86(5):591–3.
[7] Adkinson JM, Talsania JS. Ulnar nerve ligation after removal of Norplant: a case report. Hand 2013;8(1):92–6.
[8] Gillies R, Scougall P, Nicklin S. Etonogestrel implants: case studies of median nerve injury following removal. Aust Fam Physician 2011;40(10):799–800.
[9] Kang S, Niak A, Gada N, Brinker A, Jones SC. Etonogestrel implant migration to the vasculature, chest wall, and distant body sites: cases from a pharmacovigilance database. Contraception 2017;96(6):439–45.
[10] CEU statement: intravascular insertion of Nexplanon® — June 2016. The Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians & Gynaecologistshttps://www.fsrh.org/standards-and-guidance/documents/ceu-statement-intravascular-insertion-of-nexplanon-june-2016/. [Last accessed August 22, 2018].
[11] Fakier A, Petro G, Fawcus S. Mid-upper arm circumference: a surrogate for body mass index in pregnant women. S Afr Med J 2017;107(7):606–10.
[12] Benítez B, Suárez Llanos J, Fuentes Ferrer M, Oliva García J, Delgado Brito I, Pereyra-García Castro F, et al. Relationship between mid-upper arm circumference and body mass index in inpatients. PLoS One 2016;11(8):e0160480.
[13] Malnutrition Universal Screening Tool. https://www.bapen.org.uk/pdfs/must/must_full.pdf. [Last accessed February 18, 2019].
[14] Odom EB, Eisenberg DL, Fox IK. Difficult removal of subdermal contraceptive implants: a multidisciplinary approach involving a peripheral nerve expert. Contraception 2017;96(2):89–95.