New Developments in IUDs
- Copper products and the US FDA (Food and Drug Administration)

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Disclosures
• Scientific advisory boards (Bayer, OCON Medical, Teva)
• Previous product donations from Bayer, Teva, Merck for research
• Previous funding from Bayer, DuraMed for research
• Currently studying Mona Lisa product in USA
• No personal remuneration

Outline
• TCu380A
  – Aims and challenges to finding a better product
• The EU products
  – Design differences, CE marks, and regulatory
• New Developments in USA
  – New interest in IUDs
  – Products being considered
  – Product features
  – Timelines for possible FDA approval

What is the Standard for Comparison?
• The TCu380A
  – Kulier et al., Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005347
  • 35 trials, 18 comparisons of 10 different IUDs in 48,000 women
  • Found to be the best-performing copper IUD
  – Worldwide: 200 million women use the TCu380A
  – The only copper IUD with WHO specifications for standardized manufacturing
  – The only copper IUD in the USA

TCu380A: Removal for Bleeding, Pain, Expulsion

A reasonable target rate
Main Limitation of Systematic Review

- Focus on comparing discontinuation events
  - Side effects are just one cause
- Could not compare IUDs on simple incidence/prevalence of side effects
- Discontinuations for bleeding and pain are the tip of the iceberg

Tip of the Iceberg – Removals Due to Bleeding/Pain

Europe: Favorable Environment for Copper IUD Innovation

- Rich history of research and development
- About 6 basic IUD designs, with variations
- Dozens of different products currently available
- Six IUD manufacturers in Western Europe alone
- Regulated as a Class III medical device, not a drug
- CE mark and Notified Body process
- Safety: relies of review of materials, manufacturing, previous evidence, pre-clinical studies (toxicity and others)
- Generally no large-scale clinical research required
- Country-specific Health Authorities
  - Approve after marketing/pricing/surveillance negotiations
- Post-marketing surveillance: primary means of efficacy and safety confirmation

Approaches to Potentially Reduce Side Effects/Expulsions

- Eliminate frame
  - GyneFix
- Modify T-frame
  - Arms up – NovaT (Bayer)
  - Make device smaller – TT380 Short (7 Med Industrie)
  - Bend tips of arms inward (Flexi-T, Prosan)
  - Nitinol instead of plastic for frame
- Eliminate rigid perpendicular orientation of arms
  - Multiload Ml 375 and 250
- Eliminate T-frame
  - Add a 3rd dimension (Intrauterine Ball)
- Reduce copper content

What Have We Learned?

- Reduced Side Effects?
  - Very little consistent evidence either way
  - Still lacking large, blinded, randomized trials in nulliparous populations
  - Comparative trials in parous populations may be under-powered to detect benefits
  - Meticulous bleeding and pain data are lacking
    - Even minor reductions can be tremendously important to users
    - Removal for bleeding and pain is not the only measure that matters

Figure 1. IUD Use in the USA, 1965-2014

Mirena LNG-IUS
Introduced
Mona Lisa NT Cu380 Mini

**Miscellaneous Information on Product**
- Marketed in EU since 2014
- Distributed in 10+ countries
- 20% smaller than TCu380A
- No published clinical studies on product
- No quantitative data on: efficacy, side effects, or expulsions

**New Developments**
- January 2017: US FDA approval to conduct large Phase III trial

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**VeraCept™ copper IUD**

**Miscellaneous Information on Product**
- Product developed in USA
- Comparative trial in Dominican Republic
- 200 VeraCept versus 100 TCu380S
- Higher continuation rate
- Lower removal rate for bleeding/pain
- 0.3% pregnancy rate

**First FDA Study**
- US FDA approval to conduct Phase II trial

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**Intrauterine Ball™ copper IUD**

**Miscellaneous Information on Product**
- Product developed in Israel
- First marketed in EU in 2014
- Sizes A (smallest), B, and C (largest)
- A version: comparative trial completed
- Other studies completed

**Three active Clinical Trials.gov studies:**

1. NCT02779061: IUB(TM) SCu300B - Post Marketing Performance Study in Austria
2. NCT01593663: A Study to Evaluate the Safety and Initial Efficacy of a Novel Intrauterine Device – Baram et al.; Contraception 2014
3. NCT02036177: Multivariate Assessment of the IUB Intrauterine Device Compared With a T380A IUD
Intrauterine Ball™ copper IUD

Study Details
- ClinicalTrials.gov Identifier: NCT02036177
- A_version: comparative study
- 367 participants randomized
- 245 IUB_A versus 122 to TCu380A
- Bulgaria and Romania

Results: ESC Basel (2016) – Publications Pending
- Pregnancy rate: 1.1 per 100
- Expulsion rate: higher for IUB compared to TCu380A
- Lower expulsion with more experience
- Lower pain and cramps with IUB
- Possible reductions in bleeding

Conclusions
- Many copper IUDs with potential for reducing side effects
- Renewed interest in IUDs: opportunity for research
- Research approved by US Food and Drug Administration
  - Hopefully find reduced side effects while maintaining efficacy
  - Hopefully new products available in 2022 and beyond

Thank You