Endometriosis and risk of ectopic pregnancy

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- No other conflict of interest

Endometriosis

- Complex, chronic inflammatory condition
- Link with infertility well recognized
  - 2 fold higher risk of infertility after adjusting for age *(Prescott et al.2016)*
  - Increased requirement for medically assisted reproduction
- Altered peritoneal and endometrial milieu *(Giudice and Kao. 2004)*
- Molecular and functional aberrations in the eutopic endometrium

Effect of endometriosis on reproductive function

- ovarian response and oocyte quality *(Harlow et al. 1996)*
- endometrial receptivity and implantation *(Harb et al. 2013)*
- trophoblast invasion and placentation *(Brosens et al. 2012)*
- may predispose to adverse pregnancy outcomes?

Impact on pregnancy

- A surge in studies over the last 5 years exploring the impact of endometriosis on pregnancy
- Preliminary data from studies in infertile women
- Lately, an increase in number of studies using population based data
- Evidence suggestive that endometriosis has an adverse effect on pregnancy

Ectopic pregnancy

- Prevalence of 11 per 1000 pregnancies
- Maternal mortality of 0.2 per 1000 estimated ectopic pregnancy
- Significant physical and emotional morbidity
- A knowledge of risk factors is important
  - For surveillance of high risk women
  - To allow early identification and timely intervention

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Known risk factors for ectopic pregnancy

- Pelvic inflammatory disease
- Tubal infertility
- Assisted reproductive techniques
- Smoking
- intrauterine device usage

- Is endometriosis an independent risk factor for ectopic pregnancy?

Endometriosis and ectopic pregnancy

Relative scarcity of population based data

A systematic review of literature identified

- Two cohort studies *(Hjordt Hansen et al. 2014, Saraswat et al. 2016)*
- Four case control studies *(Job-Spira et al. 1993, Bunyavejchevin et al 2003, Brodowska et al. 2005, Hwang et al. 2016)*

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Cohort studies

Study	Participants	Exposed cohort	Unexposed cohort	Ectopic RR (95% CI)
Hjordt Hansen et al. 2014 Denmark	Women aged 15-49 years during1977-1982 followed until 2009	Women with a history of endometriosis (n=24,667)	Age matched women in 1:4 ratio (n=98,688)	1.9 (1.8, 2.1) ART 2.7 (1.4, 5.0)
Saraswat et al. 2016 Scotland	Pregnant women between 1981 and 2010	Pregnant women with a surgical diagnosis of endometriosis (n=5,375)	Pregnant women with no previous diagnosis of endometriosis (n=8,710)	2.7 (1.1, 6.7)

Meta-analysis

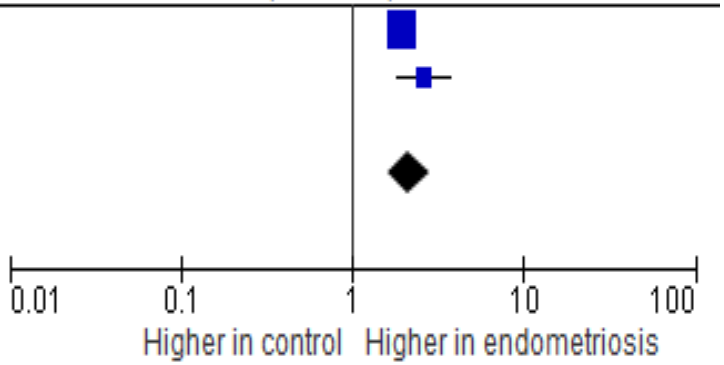
Cohort studies

Ectopic pregnancy: pooled Relative Risk (RR) and 95% Confidence Interval (CI) of 2.13 (1.62, 2.80)

	Endometriosis		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Hjordt Hansen	1076	24667	2227	98668	66.9%	1.93 [1.80, 2.08]	
Saraswat	86	5375	51	8280	33.1%	2.60 [1.84, 3.67]	
Total (95% CI)		**30042**		**106948**	**100.0%**	**2.13 [1.62, 2.80]**	
Total events	1162		2278				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.72$, df = 1 (P = 0.10); $I^2 = 63\%$

Test for overall effect: Z = 5.43 (P < 0.00001)



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Case control studies

Study	Participants	Cases (Ectopic)	Controls	Endo-metriosis OR (95% CI)
Job-Spira et al. 1993 France	Pregnant women from 15 maternities in Rhone Alps between1988 and 1991	Women with ectopic pregnancy (n=624)	Postnatal women (1:2) delivered immediately after the case was identified (n=1,247)	5.3 (2.4,11.5)
Bunyavej-chevin et al. 2003 Thailand	Pregnant women attending the hospital between 1999 and 2000	Women with ectopic pregnancy (n=208)	Women delivered on randomly selected days (n=781)	18.9 (0.9, 395.7)

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Case control studies

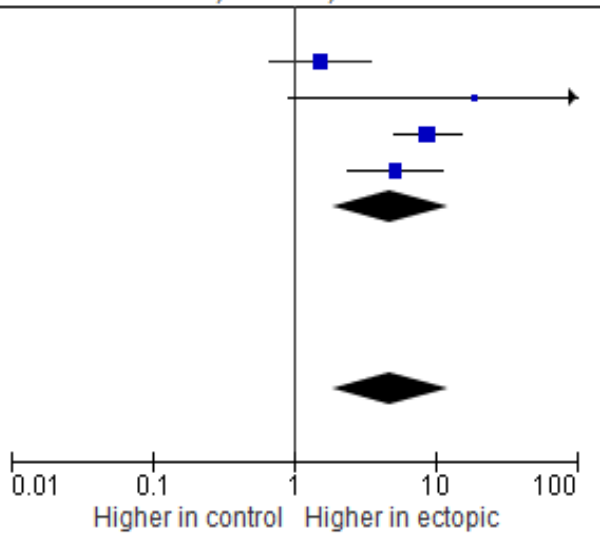
Study	Participants	Cases (Ectopic)	Controls	Endo-metriosis OR (95% CI)
Brodowska et al. 2005 Poland	Women aged 18-44 attending gynaecology department (1993-2002)	Women with ectopic pregnancy (n=214)	Women attending outpatient 1993-2002 (n=215)	1.6 (0.7, 3.5)
Hwang et al. 2016 Taiwan	Women from general population between 2003 and 2013	Women with ectopic pregnancy (n=6,637)	Age-matched women to cases in 1:2 ratio (n=13,270)	8.8 (5.1, 15.2)

Meta-analysis

Case-control studies

Ectopic pregnancy: pooled Odds Ratio (RR) and 95% CI of 4.82 (1.89, 12.31)

Study or Subgroup	Ectopic pregnancy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.2 Case control studies						
Brodowska	15	214	10	215	29.1%	1.55 [0.68, 3.52]
Bunyavejchevin S	2	208	0	781	7.6%	18.92 [0.90, 395.67]
Hwang	70	6637	16	13270	33.4%	8.83 [5.13, 15.21]
Job-Spira	23	624	9	1247	29.9%	5.26 [2.42, 11.45]
Subtotal (95% CI)		**7683**		**15513**	**100.0%**	**4.82 [1.89, 12.31]**
Total events	110		35			
Heterogeneity: Tau² = 0.61; Chi² = 12.68, df = 3 (P = 0.005); I² = 76%						
Test for overall effect: Z = 3.29 (P = 0.0010)						
Total (95% CI)		**7683**		**15513**	**100.0%**	**4.82 [1.89, 12.31]**
Total events	110		35			
Heterogeneity: Tau² = 0.61; Chi² = 12.68, df = 3 (P = 0.005); I² = 76%						
Test for overall effect: Z = 3.29 (P = 0.0010)						
Test for subgroup differences: Not applicable						



ART pregnancies

- Ectopic risk in ART pregnancies varies depending on
  - ART techniques
  - Hormonal milieu
  - Fresh vs frozen cycle
  - No. of embryos transferred
  - Innate characteristics of women – e.g. tubal infertility

- Limited data regarding association of endometriosis with ectopic pregnancy

- Extreme heterogeneity amongst studies – comparison groups, study design, primary or secondary infertility, no. of embryos transferred etc.

ART pregnancies

- Most studies in infertile women
  - did not evaluate association of endometriosis with ectopic pregnancy
  - Relatively small sample sizes

- Few studies found a positive association
  - *Clayton et al. 2006*
  - *Malak et al. 2011*
  - *Hjordt Hansen et al. 2014 (subset analysis)*
  - *Weiss et al. 2016*

- No significant association reported by
  - *Santos-Ribeiro et al. 2016*

Endometriosis and ectopic pregnancy

- Consistent evidence that endometriosis increases the risk of ectopic pregnancy irrespective of mode of conception

- Existing data not without limitations

- Only two large cohort studies *(Hjordt Hansen et al. 2014, Saraswat et al. 2016)* and one large case control study *(Hwang et al. 2016)*

Limitations of existing literature

- Misclassification bias
  - Lack of laparoscopic diagnosis of endometriosis in 5/6 studies included in the meta-analysis
  - Undiagnosed cases of endometriosis in the unexposed cohort/control group
- Lack of temporal association
  - Danish study *(Hjordt Hansen et al. 2014)* included pregnancies up to 3 years prior to the diagnosis of endometriosis
- Clustering of outcomes
  - Danish study evaluated outcomes per pregnancy allowing each woman to be counted more than once

Limitations of existing literature

- Mixture of women with spontaneous conception and ART pregnancies amongst cases and controls

- Small sample size of most case control studies *(except Hwang et al. 2016)* and poor quality.

Plausible explanation

- Distortion of pelvic anatomy
  - Stage III and IV endometriosis
  - associated subclinical tubal infertility *(Matallaiotakis et al. 2007)*

- Altered uterine activity
  - Abnormal frequency and amplitude of uterine contractions
  - Dysperistalsis promotes abnormal implantation

Plausible explanation

- Abnormal endometrial milieu for implantation
  - Impaired endometrial growth in both proliferative and secretory phase *(Bromer et al. 2009, Jones et al. 2009)*
  - Structural and molecular alterations in eutopic endometrium – altered glycosylation – attachment of the blastocyst depends on the interaction with the glycocayx of the luminal epithelium – contributory to implantation failure *(Miller et al. 2010, Brosens et al.2012)*
  - Progesterone resistance with aberration of progesterone dependent genes in the eutopic endometrium *(Burney et al. 2007, Aghajanova et al. 2009)*

Conclusions

- Endometriosis increases the risk of ectopic pregnancy
- Improve awareness amongst health professionals
- Counseling of women with endometriosis regarding early pregnancy complications
- Increased surveillance with ultrasound scans during pregnancy in women with endometriosis
  - Early ultrasound at 6 weeks recommended in both spontaneous and ART pregnancies

Barriers to research

- Defining the population with the disease – true prevalence unknown
- Need for an invasive procedure
  - Laparoscopy +/- histology - Gold standard for diagnosis
  - Beset by lack of standardization (EPHect initiative)
- Identifying the best ‘comparison’ group
- Problems with standardization of treatment or exposure

Challenges

Poorly understood natural history

- Is the disease progressive?

- Timeframe for disease development
  - is there a window that could be targeted for prevention and/or progression?

Is endometriosis a single entity?

Do different phenotypes and sites (peritoneal, ovarian, rectovaginal) behave differently?

Research opportunities

- Impact of site and stage of endometriosis on pregnancy

- Does surgical treatment of endometriosis improve pregnancy outcomes?
  - Best surgical treatment?

- Multicenter prospective cohort with standardised data collection of exposure, outcomes and co-variates

Research opportunities

- Biological markers to stratify women at higher risk of pregnancy complications
- Ascertain target areas for interventions that would minimise the adverse impact of endometriosis
- Disentangle the role of subfertility in evaluating the influence of endometriosis on pregnancy

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Thank you