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Delegado en el Consenso de Montpellier por ALMER
Vice Presidente, Sociedad Argentina de Endometriosis

Montpellier 2011 evidence based guideline on the management of endometriosis

Montpellier 2011 evidence based guideline on the management of endometriosis

Objetivo: lograr consenso acerca del manejo óptimo de la endometriosis con las herramientas de las que disponemos en la actualidad, otorgando relevancia al impacto y los resultados de los tratamiento brindados a las pacientes, con especial atención en lo referente a la efectividad de los mismos, así como al daño potencial que estos puedan causar, incluyendo información acerca del costo y la disponibilidad de estos tratamientos .

Herramientas sugeridas para la evaluación, comparación y discusión de los niveles de evidencia con los que se respaldará la información a brindar en el consenso:

ESHRE:
http://guidelines.endometriosis.org/

ASRM:
http://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Educational_Bulletins/endometriosis_and_infertility(1).pdf

http://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/Practice_Guidelines/Educational_Bulletins/Treatment_of_pelvic_pain(1).pdf

RCOG:
http://www.rcog.org.uk/files/rcog---corp/GTG2410022

SOGC:
http://www.sogc.org/guidelines/documents/gui244CPG1007E.pdf
:

Cochrane:
http://thecochranelibrary.com (search on "endometriosis")

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Preliminary programme

VENUE:	Amphithéâtre d'anatomie, Montpellier Medical School
08.00-08.50	Welcome and concept, including AGREE tool, guidelines, and consensus processes; viability of 'patient clustering' and different sub-groups of women with endometriosis in relation to their clinical management
08.50-09.10	Clinical diagnosis of endometriosis, including potential bio-markers
09.10-09.30	Cause of pain in endometriosis
09.30-09.50	Cause of infertility in endometriosis
09.50-10.10	Risk of lifestyle factors (including diet)
10.10-10.30	REFRESHMENT BREAK
10.30-10.50	The role of centres of "expertise"/specialist in the management of endometriosis
10.50-11.10	The role of support organisations in the management of endometriosis
11.10-11.30	Symptom management – empirical treatment (without surgical diagnosis)
11.30-11.50	Symptom management – surgical therapies
11.50-12.10	Symptom management – medical therapies (after surgical diagnosis)
12.10-13.00	LUNCH (preceded by photographs)
13.00-13.20	Symptom management – complementary therapies
13.20-13.40	Symptom management – emerging therapies
13.40-14.00	Fertility treatment – IUI (stimulated and un-stimulated) and IVF
14.00-14.20	Fertility treatment – surgical therapies
14.20-14.45	REFRESHMENT BREAK
14.45-15.05	Fertility treatment – adjunct therapies to ART (including medical and surgical)
15.05-15.25	Fertility treatment – emerging/newer therapies
15.25-16.00	Summary discussion of consensus/controversy, further plan, and close

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Confirmed participating societies

ESHRE
ASRM
AAGL
ESGE
ISGE
IFFS
AGES
SOGC
FIGO
SGI
ALMER
RANZCOG
Cochrane Collaboration
Endometriosis Foundation of America
European Endometriosis Liga
Endometriose Foreningen (Denmark)
Endometrioosiyhdistys (Finland)
Samtök Kvenna með Endómetríósu (Iceland)
Associazione Italiana Endometriosi Onlus (Italy)
Endometriose Stichting (Netherlands)
Endometriosis New Zealand
Endometrioseforeningen (Norway)
Fundación Puertorriqueña de Pacientes con Endometriosis (Puerto Rico)
Asociacion de Afectadas de Endometriosis de Madrid (Spain)
Endometriosföreningen (Sweden)
JOYCE Support Centre (Uganda)
Endometriosis UK
Endometriosis SHE Trust UK
Endometriosis Research Center (USA)
Endometriosis Association (USA)
World Endometriosis Society
World Endometriosis Research Foundation

Montpellier 2011 evidence based guideline on the management of endometriosis

Expertos participantes del Consenso:

Thomas D'Hooghe; Gerard Dunselman; Robert Taylor; Pamela Stratton; Charles Miller; Jim Tsaltas; Sukhbir Singh; Edgardo D Rolla; Neil Johnson; CindyFarquhar; Luk Rombauts; Carlos Petta; Karl-Werner Schweppe; Paolo Vercellini; Liselotte Mettler; Robert Shaw; Ali Akoum; Linda Giudice; Bernard Hédon; Naoki Terakawa; Hans Evers; Mauricio Abrao; Robert Schenken; David Adamson; Deborah Bush, Nicole Persson; Jan Hayslip

Directores / Coordinadores:

Neil Johnson (N.Z.) y Lone Hummelshoj (World Endometriosis Society)

Montpellier 2011 evidence based guideline on the management of endometriosis

What evidence supports IUI (stimulated and unstimulated) and IVF in the management of endometriosis-related infertility? (Edgardo Rolla)

P: Women with endometriosis and infertility
Different stages
Women with histologic confirmation and those without histology sampling
Those previously surgically treated, those not previously surgically treated and both
Women with endometriomas (but treatments for endometriomas prior to ART will be dealt with elsewhere)
Deep infiltrating endometriosis
Bowel endometriosis

I: IUI (who to treat, when, why, how to treat – stimulated, unstimulated, and who and when not to treat)
IVF – who, when, why, how and treatment limits incl how many cycles
Specially tailored protocols

C: Versus no intervention
Versus surgery
Versus other medical treatment
Role of egg donation and surrogacy

O: Live birth primary outcome
Pregnancy
Egg quality
Endometrial receptivity
Risks, burden and costs

Montpellier 2011 evidence based guideline on the management of endometriosis

19. Laparoscopic surgical removal of endometriotic lesions	
Description	Laparoscopic ablation/excision of lesions.
Mechanism of action	Surgical removal of lesions improves fertility.
Volume of evidence	Systematic review examining laparoscopic surgical removal of lesions, with pain outcomes considered: - 2 RCTs examining ablation/excision +/- adhesiolysis versus no intervention in stage 1 and 2 endometriosis. - No RCTs in stage 3 and 4 endometriosis. Observational studies of repeat surgery. Observational studies of laparoscopic surgery following failed IVF.
Consistency of evidence	Poor – the results from the 2 RCTs differed.
Applicability of evidence	Applicable.
Effectiveness	Systematic review and meta-analysis suggests fertility benefit from laparoscopic removal of endometriosis. First operations tend to produce a better response than subsequent surgical procedures, the pregnancy rates after repeat surgery being approximately half that with primary surgery.
Adverse effects	Complications of laparoscopic surgery.
GRADE – evidence quality	Moderate for primary surgery – trial results not consistent. Low for impact of repeat surgery – observational studies only. Low for laparoscopic surgery following failed IVF – observational studies only.
Consensus	
Consensus statement	**Q47:** **Laparoscopic surgical removal of endometriosis improves fertility in stage 1 and 2 endometriosis** (strong). **Q48:** **Although RCTs have failed to demonstrate benefit of excision over ablation, it is recommended to excise lesions where possible, especially where pain is present** (weak).
References	Jacobson et al (2009); Vercellini et al (2009)

20. Laparoscopic removal of endometriomas	
Description	Laparoscopic excision (or cystectomy) for endometrioma, where the entire cyst wall is completely removed. Laparoscopic ablation (or drainage/fenestration and electrocoagulation) of endometrioma, where the endometriotic cyst is opened, its contents drained and surgical electrocautery is applied to the cyst wall.
Mechanism of action	Removal of ovarian endometriotic cyst, preferably retaining as much normal ovary tissue as possible, designed to enhance fertility.
Volume of evidence	Systematic review of 2 RCTs examining laparoscopic cystectomy versus drainage and coagulation of ovarian endometriomas. Other studies have assessed the impact of ovarian surgery for endometriomas on ovarian reserve.
Consistency of evidence	Good.
Applicability of evidence	Applicable.
Effectiveness	Laparoscopic cystectomy for endometriomas ≥4cm is associated with improved fertility and lower recurrence rates compared to drainage and coagulation. If IVF is required, ovarian access may be improved and it is believed that pelvic infection rates may be reduced by prior surgery for endometriomas. Harmful effects on ovarian reserve may accompany stripping endometriomas, although there is insufficient evidence that this is worse for stripping versus drainage and coagulation. One small RCT examining suturing versus electrosurgical diathermy for haemostasis, with adhesions as outcome.

Laparoscopic cystectomy for endometriomas ≥4cm is associated with improved fertility and lower recurrence rates compared to drainage and coagulation. If IVF is required, ovarian access may be improved and it is believed that pelvic infection rates may be reduced by prior surgery for endometriomas. Harmful effects on ovarian reserve may accompany stripping endometriomas, although there is insufficient evidence that this is worse for stripping versus drainage and coagulation. One small RCT examining suturing versus electrosurgical diathermy for haemostasis, with adhesions as outcome.
Complications of laparoscopic surgery.
High.
Q49: **Laparoscopic excision (cystectomy) for endometriomas is preferred where possible to laparoscopic ablation (drainage and coagulation) to enhance fertility** (strong)
Hart et al (2011); Pellicano et al (2008).

21. Surgery for deep infiltrating endometriosis (DIE)	
Description	Conservative surgery involves removal of endometriosis that can safely be undertaken without risking surgery to the pelvic viscera. If DIE involves the bowel wall, particularly the rectum, the surgical approaches are shaving, disc excision or excision and reanastomosis. If DIE involves the urinary tract or vaginal walls, similar principles apply.
Mechanism of action	Removal of DIE designed to improve fertility.
Volume of evidence	Primarily observational studies.
Consistency of evidence	Poor.
Applicability of evidence	Difficult to apply owing to study design, poor description of disease extent including depth of penetration, heterogeneous patient populations, inconsistency of access to appropriate surgical expertise, variable radicality of surgery in the same studies, variable experience and expertise of surgeons, short follow up, poor description of dropouts, variable use of postoperative medical therapy .
Effectiveness	Suggestion of improved fertility in observational studies.
Adverse effects	Variable reports of incidence of major intra- and post-operative complications from the radical surgical approaches, ranging from 0-13%.
GRADE – evidence quality	Very low, owing to study design, as well as volume, consistency and applicability of evidence issues.
Consensus	
Consensus statement	**Q50:** **There is no clarity as to the best surgical approach to DIE in women with infertility** (weak). **Q51:** **What is clear is that highly specialised surgical expertise is required by surgeons, who undertake this kind of surgery, and it should be undertaken only within centres of expertise** (weak).
References	Chapron et al (1999); Vercellini et al (2006); Barri et al (2010).

22. Adjunct medical therapy before or after surgery for infertility	
Description	Pre- and/or postoperative adjunct hormonal medical therapy.
Mechanism of action	Designed to suppress endometriosis and enhance fertility.
Volume of evidence	Systematic review of 16 RCTs.
Consistency of evidence	Good.
Applicability of evidence	Applicable.
Effectiveness	No evidence of any fertility benefit from postoperative medical therapy. No evidence of benefit of pre- and postoperative medical therapy versus postoperative medical therapy alone (1 RCT). No trials compared preoperative medical therapy to surgery alone. No trials compared pre- and postoperative medical therapy to surgery alone.
Adverse effects	Side effects common amongst women on hormonal suppressive therapy.
GRADE – evidence quality	High.
Consensus	
Consensus statement	**Q52:** **Medical adjunct therapy in conjunction with laparoscopic surgery has not been shown to have fertility benefit** (strong)
References	Furness et al (2004).

23-a. Controlled ovarian stimulation	
Description	Letrozole versus gonadotrophins.
Mechanism of action	Different methods of stimulating ovarian follicle development.
Volume of evidence	Letrozole versus gonadotrophins: 1 RCT including 20 women.
Consistency of evidence	Minimal evidence.
Applicability of evidence	Applicable.
Effectiveness	Letrozole versus gonadotrophins: higher total number of follicles with gonadotrophins, but no evidence of a difference in pregnancy rate per completed cycle.
Adverse effects	Multiple pregnancy.
GRADE – evidence quality	Low – single very small RCT n=20.
Consensus	
Consensus statement	**Q53:** **For controlled ovarian stimulation there is no evidence to support the use of ovarian stimulation alone and insufficient evidence to recommend one agent over another** (weak).
References	Aygen et al (2010).

What evidence supports IUI and IVF in the management of endometriosis – related infertility?

IUI: Intrauterine insemination IVF: in vitro fertilization

What evidence supports IUI and IVF in the management of endometriosis – related infertility?

Edgardo D. Rolla M.D.

Endometriosis – ALMER

(Asociación Latinoamericana de Medicina Reproductiva)

Other affiliations:

- Director of Publications – IFER (Inst. de Ginecol. y Fertil.) Bs. As. - Argentina
- Vice Presidente – SAE (Sociedad Argentina de Endometriosis)
- Board Member – SACIL (Soc. Arg. de Cirugia Laparoscópica)

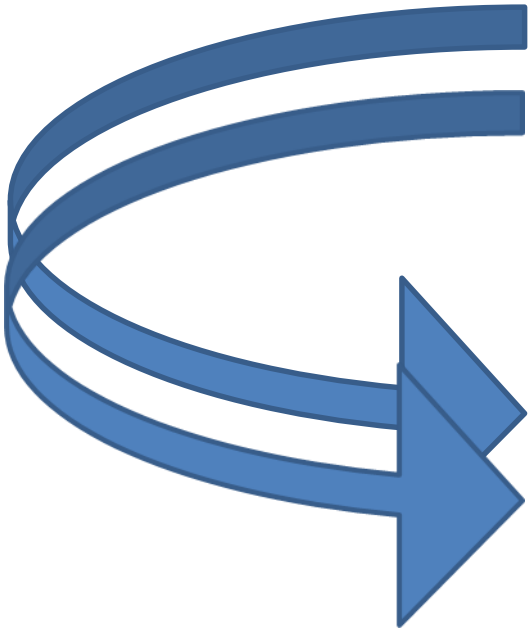
Disclosure:

- Bayer AG – registration and lodging
- Laboratorios Bagó S.A. – travel expenses
- MSD – air fare

IUI: Intrauterine insemination IVF: in vitro fertilization

Evidence supporting IUI for endo patients

To keep in mind:



- **IUI requires normal or mild male factor**
- **IUI requires patent tubes**
- **IUI requires sufficient ovarian reserve**

Issues that imply that this treatment's results correlate with the severity of the disease and/or the success of previous surgery

Evidence supporting IUI for endo patients

ESHRE GUIDELINES

Evidence level 1b

High quality

Treatment with intra-uterine insemination (IUI) improves fertility in minimal-mild endometriosis: IUI with ovarian stimulation is effective but the role of unstimulated IUI is uncertain (Tummon et al., 1997).

IUI with or without controlled ovarian hyperstimulation (COH) is associated with a higher pregnancy rate than expectant Management - Tummon, 1997 - RCT

IUI +COH significantly increased the probability of pregnancy compared to IUI alone (RR 5.1, CI 1.1-22.5) – Nulsen, 1993 - RCT

Systematic review of six trials demonstrated superiority of COH + IUI in ovulatory infertility plus endometriosis – Costello 2004 - RCT

Meta – analysis of 13 trials: conception increased by IUI – ESHRE Capri Workshop, 1996 - RCT

Endometriosis reduced by half the efFectiveness of IUI in 5214 cycles – Hughes, 1997 – Logistic regression model

Homologus insemination resulted in simmilar PR in surgically treated endometriosis and unexplained infertility after 6 cycles – Werbrouk, 2006 – Case control study

Significant improvement of PR can be expected with COH/IUI in endometriosis patients despite the negative impact of the disease

Evidence supporting IUI for endo patients

ASRM Practice Committee - Endometriosis and Infertility

HIGH QUALITY

Treatment of endo patients with COH + IUI is effective

Guzik, COH + IUI vs. no treatment = P 0.09 – Unexplained infertility including treated endometriosis - RCT
Chafkin, COH + IUI vs. COH = P0.129 – endometriosis associated infertility – RCT
Fedele, COH + IUI vs. no treatment = P 0.15 – endometriosis associated infertility – RCT
Table 1

Clomiphene Citr. + IUI in 4 cycles better than timed intercourse in treated endo - Deaton, 1990 -RCT

Treatment of endometriosis in the female partner of an infertile couple raises a number of complex clinical questions that do not have simple answers - 2006

COH: Controlled ovarian hiperstimulation

Evidence supporting IUI for endo patients

HIGH QUALITY

RCTs: **Tummon**, 1997 Fert & Steril → **Stimulated is effective**

…but the role of unstimulated IUI is uncertain

HIGH QUALITY

RCTs: **Nulsen**, 1993 Obst Gynecol → **Stimulated is more effective**

HIGH QUALITY

RCTs: **Costello,** 2004 Au N Z J O Gyn → **CC + IUI better**
HMG + IUI superior
(Syst. Review)

RCTs: randomized controlled study CC: Clomiphene C. HMG: Human Menopausal Gonadotropin

Evidence supporting IUI for endo patients

MODERATE QUALITY

PRs: **Subit**, 2011 Am J Rep Inmun → **Double IUI improves fertility in Antiendometral Antibody (+) endo pts.**

MODERATE QUALITY

RCCs: **Werbrouck**, 2006 Fert & Steril → **In min/mld endo COH + IUI = effective as in unexpl. infert.**

MODERATE QUALITY

SysRev: **Hughes,** 1997 Hum Repr → **COH + IUI useful in endo**
Endo ↓ ½ PR by COH + IUI

….one key finding of this review is that further studies are urgently needed

PR: Pregnancy rate
SysRev = Systematic review RCCs = retrospective controlled cohort study PRs = prospective registry study

Evidence supporting IUI for endo patients

LOW QUALITY

ORs: **Lodhi**, 2004 Gyn Endocrinol → **In min/mld endo COH + IUI ~ GIFT**
In mod/sev endo GIFT is better

LOW QUALITY

RAs: **Dmowski**, 2002 Fert & Steril → **3/4 cycles of COH + IUI in min/mld endo < GIFT but OK**

….6 cycles FR 41% - prognosis worst if endo more severe

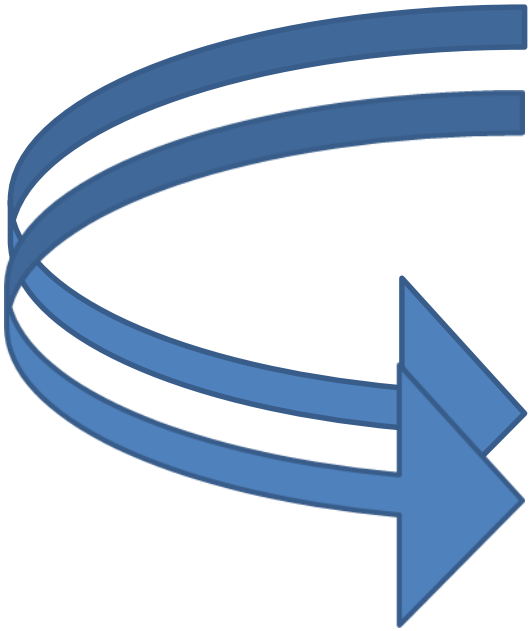
LOW QUALITY

RAs: **Lin,** 2001 J Formos Med Assoc → **COH + IUI better than post op medical treat only**

RAs = Retrospective analysis study ORs = Observational retrospective study

The role of IVF in endometriosis associated infertility

To keep in mind:



- Stage III / IV endo = inflammatory disease
- IVF requires acceptable uterine cavity
- IVF requires sufficient ovarian reserve

Issues that imply that this treatment's results correlate with the severity of the disease and/or the history and quality of previous surgeries

Evidence supporting IVF for endo patients

ESHRE GUIDELINES

Evidence level 1a **High quality**

IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility (Barnhart et al., 2002).

Evidence level 2b **Moderate quality**

In vitro fertilization (IVF) is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed

Evidence supporting IVF for endo patients

ESHRE GUIDELINES

Evidence level 1b **High quality**

Treatment with a GnRH agonist for 3-6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However the authors of the Cochrane review stressed that the recommendation is based on only one properly randomized study and called for further research, particularly on the mechanism of action (Sallam et al., 2006).

Evidence level 1b **High quality**

Laparoscopic ovarian cystectomy in patients with unilateral endometriomas between 3 and 6 cm in diameter before IVF/ICSI can decrease ovarian response without improving cycle outcome (Demirol et al., 2006).

Evidence supporting IVF for endo patients

ESHRE GUIDELINES

Evidence level 2a **Moderate quality**

Risk for recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyper stimulation for IVF (D´Hooghe et al., 2006).

GCP **Very low quality**

Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥ 4 cm in diameter is present to confirm the diagnosis histologically; reduce the risk of infection; improve access to follicles and possibly improve ovarian response. The woman should be counseled regarding the risks of reduced ovarian function after surgery and the loss of the ovary. The decision should be reconsidered if she has had previous ovarian surgery.

Evidence supporting IVF for endo patients

ASRM Practice Committee - Endometriosis and Infertility

HIGH QUALITY

IVF better than EM …..*but no new and large RCTs to confirm*

Soliman, 1993 Fertil & Steril – EM = 0% PR (n=6)– IVF 33% PR (n=15) - RCT

Long term GnRH agonist suppression improves PR in severe endo

Surrey, 2002 Fertil & Steril – 3 months GnRH treat. vs. reg. COH = 80% vs. 53.85% ongoing PR - RCT

But there is no unanimous strategy consensus

Evidence supporting IVF for endo patients

HIGH QUALITY

RCTs: **Bianchi,** 2007 Fert & Steril → **Deep endo laparosc. surgery does not improve IVF results**

…..and more ovulatory drugs required for a smaller total # of oocytes

HIGH QUALITY

RCTs syst. review: **Benschop,** 2010 Cochrane →

Agonists vs. antag. = PR

Ag. better ov. response vs. ant.

Cystec. or drain + coag. = EM

Cystec. vs. drain + coag. = PR

Cystec. vs. drain + coag. = NMO

….4 studies - 312 pts. included

….no reference to live births

EM: expectant management PR: pregnancy rate NMO: number of mature oocytes

Evidence supporting IVF for endo patients

MODERATE QUALITY

RCTs: **VAR T,** 2011 Fert & Steril → **Laparosc. cystect. signif. ↓ ovarian response for IVF vs. drain + coagulation**

…..but the "n" of patients treated suggest more studies should be done

…..and no reference for live births is included

MODERATE QUALITY

PNRs: **PIVER,** 2003 Fert & Steril → **Adenomiosis by MRI (-) for IVF**

↑ Junction zone thickness = ↓ PR

….compares 37% PR in adenomiosis vs. 50% in normal (Total "n" = 97)

PNRs: Prospective non randomized study MRI: magnetic resonance imaging

Evidence supporting IVF for endo patients

MODERATE QUALITY

MCCs: **Días**, 2000 Fertil & Steril → **In egg donation program IR, PR and MR = in endo or non endo patients**

…. 28% live births in endo (25 pts.) - 27.2% in non endo (33 Pts.)

MODERATE QUALITY

PNRTs: **Gianaroli,** 2010 Hum Reprod → **Aneuploidy in IVF oocytes more frequent in endo pts.**

…. inverse and significant correlation was found between the proportion of normal oocytes and (i) female age, (ii) ….endometriosis….

MODERATE QUALITY

RA:s **Simon,** 1994 Hum Reprod → **recipients of embryos from endo ovaries had ↓ IR (P< 0.05)**

PNRTs: prospective non randomized trial RAs: Retrospective analysis

MCCs: matched case-control study IR = implantation rate PR = pregnancy rate MR = miscarriage rate

Topics for discussion

P:	**women with endometriosis associated infertility** **with / without histological confirmation** **with / without previous surgeries** **different stages** **endometrioma** **deep infiltrating endo**
i:	**IUI - who to treat, when, how to treat – stimulated** **IVF – who, when, how to treat** **specially tailored protocols** **oocyte donation**
C:	**Vs. no intervention** **Vs. surgery** **Vs. other causes of infertility**
O:	**egg quality** **fertilization** **endometrial receptivity** **implantation** **pregnancy** **live birth**