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The role of *Escherichia coli* in reproductive health: state of the art

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Abstract

Escherichia coli is a well-known commensal of the normal intestinal microbiome that can also colonize the vaginal microbiome, usually without symptoms. However, *E. coli* can also be a highly virulent and frequently deadly pathogen. In this review, I will discuss the role *E. coli* has in reproductive health and disease.

Keywords: *Escherichia coli*; Neonatal sepsis; Stillbirth; Maternal sepsis; Infertility

1. Introduction

Few microorganisms are as versatile as *Escherichia coli. E. coli* is a well-known commensal of the normal intestinal microbiome that sometimes colonizes the vagina, usually without symptoms. However, *E. coli* can also be a highly virulent and frequently deadly pathogen.

In this review, I will discuss the role of *E. coli* in adverse pregnancy outcomes.

2. *E. coli* and infertility

Infertility is defined as the lack of conception after at least one year of constant unprotected sexual intercourse [1], and is a worldwide increasing medical problem seen in 13–15% of reproductive age couples [2]. *E. coli* can affect both female and male fertility.

Pelvic inflammatory disease (PID) is an infection-induced inflammation of the female upper reproductive tract that can result in reproductive disability such as infertility due to damage of the Fallopian tube(s) [3,4]. In more than 85% of PID cases, the etiological agent are sexually transmitted pathogens or bacterial vaginosis-associated bacteria [3]. *E. coli* is part of the remaining 15% of infectious agents that consist of enteric and respiratory pathogens [3].

About 15% of cases of male infertility are caused by male genital tract infections, including epididymitis, orchitis and prostatitis, but no data on the relative contributions of these infections are known [1,5]. Epididymitis- and orchitis-induced infertility, although rare [1], are commonly caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in men between 14 and 35 years of age. In other age groups, common urinary tract pathogens such as *E. coli* predominate [1,6]. *E. coli* is involved in up to 80% of total acute or chronic prostatitis cases [1,7].

Spermatozoa themselves can be affected by urogenital infections or colonizing bacteria [1]. In vitro, *E. coli* has been shown to rapidly and irreversibly adhere to spermatozoa, resulting in agglutination, altered morphology, immobilization and impaired fertilization [8,9]. *E. coli* strains that had been shown to cause agglutination of human sperm can also cause infertility in mice [10]. In a clinical study, the presence of vaginal *E. coli* was an independent risk factor for pregnancies conceived through infertility treatment (i.e. intra-uterine insemination or in vitro fertilization) compared to natural pregnancies [2]. Another clinical study showed that treatment and subsequent clearance of *E. coli* from sperm before in vitro

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fertilization was associated with higher pregnancy rates compared to sperm positive for *E. coli* at the time of in vitro fertilization, although the absolute numbers of patients were too small to draw conclusions [11]. A comparison between fertile and infertile patients concerning the prevalence of *E. coli* and/or enterococci in semen did not reveal significant differences [12].

3. *E. coli* and miscarriage

Miscarriage is one of the most common yet under-studied adverse pregnancy outcomes. It is often defined as the spontaneous loss of pregnancy in the first 22 weeks of pregnancy, although there is no universal consensus on the cutoff used [13–15]. Early miscarriage occurs in the first 3 months of pregnancy, while late miscarriages occur after three months of pregnancy but before 24 weeks, although definitions vary between countries, local practices and studies [16]. Up to one in five pregnancies ends with an early miscarriage, while late miscarriage (also named second-trimester or mid-trimester miscarriage) is less common and occurs in 1–2% of pregnancies [16,17].

Although the etiology of miscarriage is often unknown, it has been estimated that potentially preventable infections account for up to 15% and 66% of early and late miscarriages, respectively [18–20].

In one study, 77% of the 101 cases of late miscarriage (median gestation of 19 weeks, range 16–22 weeks), but none of the 103 controls of medically induced abortions, had histological chorio-amnionitis [18]. The majority of isolates of the culture-confirmed cases were mycoplasmas and streptococci, whereas *E. coli* was isolated in 3% of cases.

McDonald and coworkers [21] studied 129 cases of spontaneous fetal losses (ranging between 16 and 26 weeks of gestation) and their respective placentas. In 85 (66%) cases, bacteria were recovered from the placenta and/or fetus, whereby *E. coli* was isolated in one fourth of cases, occurring as the sole organism in eight cases.

4. *E. coli* and stillbirth

Stillbirth can be defined as the loss of pregnancy after 22 weeks of gestation, or by a birthweight of $\geq$500 g, although – as for miscarriage – there is no universal definition, complicating comparisons of studies [15]. Stillbirth is one of the most common causes of pregnancy loss in spite of advances in perinatal medicine, with an estimated 3.2 million cases occurring worldwide annually [22]. Rates are 3 per 1000 births in developed countries, but can approach 45 per 1000 in some developing countries [23].

Although, in 12–50% of cases, no evident cause of death can be determined, maternal or fetal infections cause 10–25% of stillbirths, a percentage that is likely to be underestimated [24,25]. Infection is more clearly associated with early stillbirth (22–28 weeks) than with late stillbirth (after 28 weeks) [26].

In developed countries, an ascending bacterial infection leading to chorio-amnionitis (intra-amniotic infection), before or after membrane rupture, is usually the most common infectious cause of stillbirth and represents a unique situation, in which two individuals are exposed to the same infection at the same time and where maternal as well as fetal responses may occur [27]. *E. coli* is considered to be the most common organism associated with stillbirth (although there are no published numbers), although, in areas where syphilis is prevalent, up to half of all stillbirths may be caused by this infection alone [22].

Determining the relationship between maternal infection and stillbirth is often challenging, and finding organisms in the placenta or on the fetus does not prove causality [22]. However, the evidence that amniotic fluid infection is causal for stillbirth comes from different studies. Placental histology has been compared in stillbirths and various control groups and, in most cases, the frequency of histological chorio-amnionitis in the stillbirth group is several times greater than in the control group(s) [22]. Even more convincing is the finding of microorganisms in internal fetal organs or placentas: cultures from interior sites such as brain, liquor, lung, liver, cardiac fluid and/or placentas, obtained at sterile autopsy, are less likely to be contaminated by vaginal microbes and are more likely to yield the etiological agent of an intrauterine infection [28]. Such findings have been described in several case series and case–control studies, and have confirmed *E. coli* intrauterine (subclinical) infection as a major contributor to intrauterine fetal mortality (Table 1) [24,27–33].

5. *E. coli* and spontaneous preterm labor

Accumulating evidence suggests that spontaneous preterm labor is a syndrome attributable to multiple pathogenic processes, including intra-amniotic infection, which is the only process causally linked to spontaneous preterm delivery [34,35]. Bacteria that ascend into the amniotic cavity can stimulate production of chemokines, cytokines, proteases and inflammatory mediators, which can initiate myometrial contractility [35].

Several studies have shown a significant association between the recovery rate of *E. coli* from (cervico)vaginal cultures and preterm labor [36–38].

6. *E. coli* and preterm rupture of membranes

In approximately 8–10% of pregnancies, fetal membranes will rupture before the onset of labor [39]. When this occurs at 37 weeks or later, this premature rupture of the membranes (PROM) is an easy-to-manage complication of a normal birth. PROM occurring before 37 weeks is defined as preterm premature rupture of membranes (PPROM) [34], and is rarer. PPROM is difficult to manage and responsible for as many as 20% of perinatal deaths [39]. In most PPROM cases, the cause is unknown, but (subclinical) intrauterine infection is a frequent precursor [34,40]. Since the fetal membranes generally form a barrier to ascending infection, intrauterine