Ovarian phenotypes impact fertility and pregnancy outcomes

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In this ovarian health focus, Adjunct Assistant Professor Zhongwei Huang, Dr. Paula Benny and Ms. Hui Wen Tam explore how ovarian phenotypes affect ovarian function and lifespan, leading to complications in pregnancy outcomes

Ovarian health has a significant impact on fertility and pregnancy outcomes, with the ovary having primary functions of oogenesis and steroidogenesis (estrogen and progesterone production), to ensure a normo-ovulatory phenotype in women. However, ovarian phenotypes derived from polycystic ovary syndrome (PCOS), premature ovarian insufficiency (POI), diminished ovarian reserve, ovarian cysts, and ovarian endometriomas affect ovarian folliculogenesis and the ovarian ultrastructure. Importantly, these direct effects on ovarian function and lifespan will affect chances of spontaneous conception and lead to pregnancy complications.

Ovarian phenotypes – unique ovarian conditions based on ovarian function

Normo-ovulation (regular ovulation) is the process by which a mature egg is released from the ovary each month. Ovulation and adequate luteal phase lengths (duration of progesterone production) are essential for fertility [1]. Women with normal ovarian function have an antral follicular count between 7-9 at baseline ultrasound assessment, whereas women with ovarian conditions such as PCOS or POI typically have higher (≥12 in PCOS) and lower (≤5 in POI) follicular counts [2,3], respectively.

The current gold standard and only clinically accepted diagnostic marker of ovarian reserve is Anti-Müllerian hormone (AMH), a glycoprotein which regulates ovarian follicular growth. Blood AMH levels peak at puberty and gradually decline with ovarian ageing. In diagnosing conditions such as PCOS, AMH levels are usually elevated due to the increased number of antral follicles. Conversely, AMH levels are markedly low (<0.075–3 pmol/l) in women with POI [4].

Polycystic ovary syndrome

PCOS is characterised by menstrual irregularity, hyperandrogenism, and polycystic ovarian morphology, based on the commonly used Rotterdam criteria. Studies have shown that the reproductive lifespan of women with PCOS is enhanced, with delays in ovarian ageing, as compared to normo-ovulatory women of the same age [5].

Women with PCOS have significantly higher AMH levels as compared to controls (44.4 vs. 18.5 pmol/L, p<0.001). While women without PCOS show an age-associated decline in AMH, women with PCOS maintain relatively high AMH levels even at older age [6].

The estimated age at menopause was later in women with PCOS (51 years), compared to controls (49 years), showing that women with PCOS may have, on average, a reproductive lifespan about two years longer than normo-ovulatory women.

In addition, recent studies have shown that Asian women with PCOS and especially those of advanced maternal age (>36 years old) have improved reproductive outcomes when undergoing assisted reproductive treatments (ART) [6].

Premature ovarian insufficiency

POI is associated with premature menopause (before the age of 40), where a woman's ovarian function is impaired. Menopause reflects an exhaustion of ovarian follicles, resulting in hypoestrogenemia, elevated follicle-stimulating hormone (FSH) levels, and a cessation of menstrual cycles.

Unlike normal menopause, which occurs around 50 years of age, women with POI experience early cessation of reproductive health, often accompanied by symptoms such as irregular or no periods, raised serum gonadotropins, and infertility due to an accelerated loss of ovarian follicles way before the normal age of menopause.

Ovarian endometriomas and cyst

Ovarian endometriomas, or "chocolate cysts," are non-malignant ovarian cysts containing old menstrual blood that affect ovarian health and fertility by reducing oocyte quality and quantity. They are notable for their impact on quality of life and the potential lifelong risk of malignant transformation.

Women with endometriomas exhibit up to 30% lower levels of AMH, a significant reduction in antral follicle count, and elevated FSH levels [7]. Larger cysts cause proportionally more damage to ovarian function, resulting in subfertility. Recent research suggests that fertility preservation through oocyte vitrification may be considered for women with bilateral endometriomas or a reduced baseline ovarian reserve [8] and who have not yet conceived.

Understanding the etiology of endometriomas can improve our understanding of why these cysts vary so much between individuals. This knowledge can support personalised treatments and guide future research to improve care for women with endometriosis [9].

Pregnancy and reproductive outcomes

Ovarian health is paramount to a healthy pregnancy as it determines oocyte (egg) quality, which ultimately determines embryo quality and development. As ovarian health and lifespan are closely associated with reproductive health, these factors significantly impair

female reproductive health by altering intricate biological mechanisms, resulting in reproductive complications.

For example, women with PCOS who often have high AMH levels generally face challenges in conceiving due to anovulatory cycles and an increased risk for pregnancy complications, including miscarriage, gestational diabetes mellitus (GDM), preeclampsia, and preterm delivery [10].

Furthermore, women with endometriosis are at an increased risk of pregnancy complications such as ectopic pregnancies, placenta previa, and miscarriage [11]. Hence, commonly encountered pregnancy complications can be a result of maternal ovarian health, which also carries the risk of affecting their female offspring's ovarian health.

Preeclampsia

Preeclampsia is characterised by the onset of hypertension after 20 weeks of gestation, accompanied by proteinuria or organ dysfunction. It endangers pregnancy through disrupting placental function and vasculature, making it the leading cause of maternal and fetal morbidity and mortality.

In women with PCOS, higher AMH levels (>9.30 ng/ml) were associated with an increased risk of gestational hypertension following IVF (fresh embryo transfer) [12]. The risk of future cardiovascular disease was also increased sevenfold in women with preeclampsia [13].

Intrauterine growth restriction and macrosomia

Intrauterine growth restriction (IUGR) and macrosomia are both pregnancy complications that have lasting effects on ovarian health. IUGR is caused by placental insufficiency and increases the risk of preterm birth and neonatal morbidity.

Female offspring born small for gestational age showed lower AMH levels and fewer antral follicles in adulthood, suggesting a reduced ovarian reserve and a higher chance of earlier menopause. Conversely, macrosomia, often caused by maternal hyperglycaemia, increases the risk of cesarean delivery [14,15].

Gestational diabetes mellitus

GDM arises due to consistently high blood sugar levels during pregnancy. GDM complicates maternal and fetal health and may also indicate subtle impairments in ovarian function. Studies on women with pre-existing type 2 diabetes show reduced AMH levels and poorer outcomes following ART compared with non-diabetic women, suggesting that maternal hyperglycemia accelerates the decline in the ovarian follicle pool and impairs egg quality [16].

Furthermore, higher AMH and insulin in the cord blood of infants born to diabetic mothers suggest that the diabetic intrauterine environment can affect early ovarian development in female offspring [17]. This connection highlights how important it is to maintain good

glycaemic control before and during pregnancy, to safeguard maternal ovarian health and the future reproductive potential of her children.

Preterm birth

Preterm birth (<37 weeks) impacts the ovarian health of mothers and daughters. Pregnant women with PCOS (AMH >9.30 ng/ml) have a 12.9% risk of preterm delivery as compared to 7.4% in control women [18]. High AMH in PCOS fertility treatments doubles preterm birth risk, likely from excessive ovarian hormones triggering early labour via inflammation.

Daughters born preterm or with a low birth weight have a 15% higher risk of POI, as IUGR reduces ovarian follicle development and increases atresia. This highlights the need to optimise maternal ovarian health before conception, monitor high-risk pregnancies, and ensure long-term reproductive follow-up to address future health conditions.

Summing up, maintaining ovarian health preserves fecundability and the chances of a healthy pregnancy. While ovarian health is imperative for reproduction, it is also tightly linked to overall health span and impacts the next generation's ovarian health and lifespan.
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