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REVIEW

A design thinking approach to primary ovarian insufficiency

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ABSTRACT

Most clinicians are not prepared to provide integrated personal care to address all the clinical needs of women with primary ovarian insufficiency. Design thinking is an engineering methodology used to develop and evaluate novel concepts for systems operation. Here we articulate the need for a seamlessly integrated mobile health system to support genomic research as well as patient care. We also review the pathophysiology and management of primary ovarian insufficiency. Molecular understanding regarding the pathogenesis is essential to developing strategies for prevention, earlier diagnosis, and appropriate management of the disorder. The syndrome is a chronic disorder characterized by oligo/amenorrhea and hypergonadotropic hypogonadism before age 40 years. There may be significant morbidity due to: 1) depression and anxiety related to the loss of reproductive hormones and infertility; 2) associated autoimmune adrenal insufficiency or hypothyroidism; and 3) reduced bone mineral density and increased risk of cardiovascular disease related to estrogen deficiency. Approximately 5% to 10% of women with primary ovarian insufficiency conceive and have a child. Women who develop primary ovarian insufficiency related to a premutation in *FMR1* are at risk of having a child with fragile X syndrome, the most common cause of inherited intellectual disability. In most cases of spontaneous primary ovarian insufficiency no environmental exposure or genetic mechanism can be identified. As a rare disease, the diagnosis of primary ovarian insufficiency presents special challenges. Connecting patients and community health providers in real time with investigators who have the requisite knowledge and expertise would help solve this dilemma.

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Intuition will tell the thinking mind where to look next.
Jonas Salk

There is a need to close the gap between knowledge and action for women with primary ovarian insufficiency (POI). To provide ideal care for each patient with POI,[1, 2] clinicians need to respect patient preferences and values and integrate them in a shared decision making process. Effective clinicians apply medical evidence in this context. Thus, evidence-based medicine is also patient-centered medicine.[3] In other words, the patient needs to be at the center of our clinical care and research efforts. Mobile health (mHealth) provides

health care remotely by employing modern telecommunications systems such as smartphones and the Internet. This technology has the potential to transform health care and biomedical research.[4] The fundamental aims of mHealth are to increase access to health care and make it more convenient.

Transitioning from traditional methods of distributing health care to a mHealth system is a huge multidisciplinary challenge. Design thinking is an engineering approach which relies on collaboration within multidisciplinary teams to provide diverse perspectives, rapid prototype creation, iterative development, and a concept of operations for the overall venture. Design thinking applies resources to meet the needs of the customer or patient rather than the needs of the organization or company.[5] As such, design thinking should be an ideal methodology with which to build a sustainable mHealth system.[6] Connecting patients and community health providers in real time with investigators who have the requisite knowledge and expertise in POI would improve access to highly specialized care and increase convenience for all. Such a system would also provide a platform from which to support community oriented genomic research and an associated Clinical Research Integration Special Program (CRISP) centered on women with POI[7]. The bottom line is all stakeholders benefit.

There is a need to make the patient's record of care available to the patient and the integrated team via a common set of communication protocols. This commonality will transform the existing complex and segregated infrastructure of proprietary or heavily customized applications into a universal system. A readily accessible single record with access controlled by the patient puts the patient at the center of the entire enterprise. Moreover, advances in cloud architecture are needed to ensure the privacy and security of the data, and provide reliability and accessibility.

Patient perspective

One of us (LAM) is a patient living with POI. As a professional advocate in the healthcare industry I know all too well the barriers that patients face on their journey to wellness. When I turned twenty-two I experienced a miscarriage. From then on I was never the same. I went extended lengths of time without menstruating, experienced intense night sweats and heart palpitations, inexplicable mood swings and crying spells. What was this storm raging within me? This was the mystery that would take eight long and uncomfortable years to solve. I survived too many physician visits, too many unnecessary medications, and too many patient dismissals before finally getting the official diagnosis of ovarian "failure." The journey didn't end there. I next saw a university specialist. We had different goals. Their focus was infertility. My focus was wellness, health, and feeling whole again. Needless to say, I was thrilled to learn of a study at the National Institutes of Health Clinical Center. This multidimensional program addressed all of my concerns and more. I came into the program with much angst and left there with a sense of peace. I was heard and validated and provided with the information to move forward in life knowing that I can be well again.

Many patients with the symptoms of "early menopause" feel despair and disconnection from having a disease their health care providers are often slow to diagnose, unable to explain the etiology, or reverse.[8] Disturbance in menstrual pattern is the most common initial symptom in women with POI.[9] As evidence of the existing knowledge to action gap for women with POI, over half of women with this complaint reported visiting a clinician's office three or more times before laboratory testing was performed to determine the diagnosis. Over half of them reported seeing three or more clinicians before diagnosis. In 25% of women it took longer than 5 years for the diagnosis to be made. Women with POI see a need for more aggressive evaluation of oligo/amenorrhea.[9] They also see a need for an approach which empowers women with the needed knowledge and tailored guidance. Such an approach must: 1) be available and accessible to women regardless of geography or socioeconomic status; 2) bring together diverse perspectives, including a wide array of medical fields, therapists and spiritual care counselors, in an integrated fashion; and 3) be developed with the individual patient foremost in mind, and tend to her at each life stage.[8]

Normal ovarian function

The ovary functions as both an endocrine organ and a reproductive organ. Ovarian function is dependent on the presence of functional primordial follicles. These are microscopic structures, each containing an oocyte.

The ovary is unique in the endocrine system in that an entirely new secretory structure develops each month. This structure is known as the Graafian follicle, which arises from a primordial follicle. The transition from a non-growing primordial follicle to a small growing (primary) follicle is called primary recruitment.[10] In secondary recruitment, with the onset of puberty, FSH stimulates macroscopic ovarian follicle growth and production of estradiol. With maturation of the hypothalamus regular ovulatory menstrual cycles begin. Menopause, defined as the permanent cessation of menses, results from the depletion of potentially functional primordial follicles. The mean (±SD) age at the time of menopause is 50±4 years.[11] Menopause before age 40 years is considered premature.

Primary ovarian insufficiency

POI differs from normal menopause. Menopause signals the permanent cessation of menses and fertility. Most women with POI have potentially functional follicles remaining in their ovaries, and intermittent ovulation with an associated subsequent menses is common. A prospective evaluation demonstrated the presence of ovarian follicles in nearly 75% of women.[12] Over a 4 month observation period about 20% of women with POI will ovulate.[13] About 5 to 10% of women conceive and deliver a child after getting the diagnosis.[14] Thus, "primary ovarian insufficiency" is the preferred term for the condition that was previously referred to as "premature menopause" or "premature ovarian failure." The term is more scientifically accurate and less stigmatizing to young women. The disorder in reality is a continuum of impaired ovarian function rather that a dichotomous state.[15, 16]

POI affects approximately 1 in 10.000 women under age 20, 1 in 1.000 women under age 30, and 1 in 100 of those under age 40. The diagnosis of POI is made in women younger than 40 years of age who have had oligo/amenorrhea for 4 or more months and who have two serum FSH levels (obtained at least 1 month apart) in the menopausal range.[17] Many women with POI develop symptoms of estrogen deficiency, to include vasomotor symptoms (hot flashes and night sweats), sleep disturbance, and dyspareunia related to vaginal dryness. However, many other women with POI have ongoing intermittent and unpredictable ovarian function, intermittently have serum estradiol levels in the normal range, and do not experience profound estrogen deficiency or the associated symptoms.

Mechanism

The cause of POI remains a mystery in 90% of cases. The condition occurs through two major mechanisms: follicle dysfunction and follicle depletion.[17] Most cases are on the basis of follicle dysfunction. Follicle dysfunction means follicles are still present in the ovary, but a pathologic process prevents their normal function. Examples of mechanisms impairing follicle function include an FSH-receptor mutation,[18] autoimmune lymphocytic oophoritis,[19] and inappropriate follicle luteinization. POI can also occur on the basis of primordial follicle depletion, but the absence of remaining follicles cannot be proven, even by ovarian biopsy (because of sampling error). There are cases of pregnancy occurring after ovarian biopsy demonstrated no follicles.[20]

Chromosomal

Turner syndrome is a congenital condition that affects 1/2500 to 1/3000 live births. The disorder is associated with POI, lack of pubertal development, associated primary amenorrhea, short stature, cognitive deficits, body malformations, and infertility. There is a wide spectrum of physical and functional abnormalities due to the wide variation in karyotypic abnormalities, ranging from 45,X (50% of cases) to various forms of 45,X/45,XX mosaicism.[21, 22] In Turner Syndrome primordial follicle apoptosis is accelerated from the second trimester of fetal life, which leads to oocyte depletion in most cases prior to the expected age of puberty.[23, 24]

Steroidogenic cell autoimmunity

Autoimmune oophoritis, the mechanism in about 4% of women with POI,[19] is characterized by a selective mononuclear cell infiltrate into the theca layer of developing follicles due to steroid cell autoimmunity (SCA-POI).[25] The selective destruction of theca cells with the relative sparing of granulosa cells leads to low estradiol levels because of a lack of androstenedione substrate produced by theca. In contrast, in women with SCA-POI, serum inhibin levels — a product of the granulosa

cells — are generally increased compared to normal controls and women with other causes of POI. Also, approximately two-thirds of women with recently diagnosed SCA-POI have normal serum AMH (antimüllerian hormone) levels, a hormone secreted by small growing follicles. This means SCA-POI is likely associated with a preserved pool of primordial follicles, and is consistent with histologic evidence that primordial follicles, lacking a theca, are spared the autoimmune attack.[19]

Genetic

Most cases of POI occur sporadically. In approximately 10-15% of cases there is a positive family history with an affected first-degree relative.[26] Strong evolutionary pressure weighs against genes limiting fertility remaining in the gene pool. To date, no single genetic mechanism has been shown to be a common cause of POI. The situation appears to be similar to the genetics of deafness, for which more than 120 independent genes have been implicated.[27] Genetic evaluation and counseling in the case of deafness is further complicated in that in some cases recessive mutations at two different loci explain the disorder. Here we review a few genetic mechanisms of POI. To fully and accurately define the genetic mechanisms of POI will likely require large-scale medical sequencing on large populations of girls and women. More extensive reviews of the genetics of POI are available.[17, 28, 29]

FMR1

The Fragile X Mental Retardation 1 gene (*FMR1*) is located at Xq27.3. Fragile X syndrome, the most common cause of inherited intellectual disability, is an X-linked CGG trinucleotide repeat disorder. In the presence of a full mutation (>200 repeats) the promoter region is silenced by methylation, causing mental retardation related to a deficiency of the protein FMRP. Women carrying the full mutation have a normal reproductive life.[30] Women who carry the premutation (55-200 CGG repeats) are at increased risk of developing POI, termed fragile X associated POI (FXPOI).[31] Premutation carrier status has also been associated with the development of a neurodegenerative disorder known as fragile X-associated tremor/ataxia syndrome (FXTAS), characterized by ataxia, tremor, dementia and Parkinson-like symptoms.[32] Interestingly, *FMR1* premutation carrier status is associated with increased production of *FMR1* mRNA. Evidence supports a conclusion that the mechanism causing FXTAS and FXPOI is a toxic gain of function of *FMR1* mRNA. In a mouse model the presence of the *FMR1* premutation is sufficient to cause POI, with the associated reduction in follicle number and fertility.[33] About 20% of women who carry the *FMR1* premutation develop FXPOI.[34]

AIRE

Autoimmunity against the oocyte protein MATER has been identified as a new mechanism of autoimmune POI in the context of a rare disease. MATER was first identified in a neonatally thymectomized mouse model of autoimmune oophoritis,[35, 36] and the protein has been shown to play a critical role in early embryonic development.[37] The rare disease autoimmune poly-endocrine syndrome type 1 (APS-1) is a multi-organ autoimmune disorder caused by mutations in the autoimmune regulator gene *AIRE*.[38] The clinical disease manifests a classic triad of hypoparathyroidism, adrenal insufficiency, and mucocutaneous candidiasis. Importantly, MATER (NALP5) autoantibodies are associated with the presence of POI in women with APS-1.[38] Autoimmune POI develops as part of APS-1 in about 30% of women. While MATER (NALP5) autoantibodies are common in women with APS-1, recent research has demonstrated they are rarely present in women with POI not associated with APS-1.[39]

GALT

Mutations in *GALT* (galactose 1-phosphate uridyl transferase) cause galactosemia, an inborn error of metabolism.[40] GALT is a key enzyme in galactose metabolism, particularly important in the neonatal period due to the ingestion of galactose-containing milk. In classic galactosemia acute symptoms generally appear soon after birth. Dietary restriction of galactose can resolve the acute and life-threatening complications, but does not fully prevent the development of serious long-term complications such as cognitive and neurologic abnormalities and POI. Approximately 80% of girls and young women with classic galactosemia experience POI despite neonatal diagnosis and rigorous dietary restriction.[41] The underlying mechanism is unclear.

FOXL2

This gene encodes a forkhead transcription factor. The gene is expressed in developing eyelids and in fetal and adult ovaries. Mutations in this gene cause the blepharophimosis-ptosis-epicanthus-inversus syndrome (BPES).[42] It is characterized by eyelid malformations and minor craniofacial abnormalities. There are two types of BPES. In BPES 1 the disorder is associated with POI. In BPES II the craniofacial stigmata are isolated. More recently mutations in this gene have been associated with ovarian granulosa cell tumors.[43] *FOXL2* plays a central role in ovarian development and maintenance. In the ovary *FOXL2* is involved in the regulation of steroid metabolism, apoptosis, reactive oxygen species detoxification and cell proliferation.[43]

MCM8, MCM9

These genes belonging to the minichromosome maintenance (MCM) protein family. These proteins are required for eukaryotic DNA replication initiation. MCM8 participates in homologous recombination and dsDNA break repair. Exome sequencing has revealed an *MCM8* pathologic variant to be associated with POI in 3 sisters who presented with primary amenorrhea, hypothyroidism, and hypergonadotropic hypogonadism.[44] The sisters were born to parents who are first cousins. Compared with fibroblasts from unaffected daughters, chromosomal break repair was deficient in the affected individuals. Thus, *MCM8* pathologic variation is associated with endocrine dysfunction and genomic instability. In a separate report, whole exome sequencing studies in two unrelated consanguineous families with daughters exhibiting primary amenorrhea, short stature, and a 46,XX karyotype revealed pathogenic variants in *MCM9*.[45] Repair of chromosomal breaks was impaired in lymphocytes from affected, but not unaffected individuals in both families. This is consistent with *MCM9* function in homologous recombination. Thus, autosomal-recessive variants in *MCM9* cause a genomic-instability syndrome associated with POI and short stature.

BMP15

The bone morphogenetic protein (BMP) family is part of the transforming growth factor-beta superfamily, which includes large families of growth and differentiation factors. Mouse *Bmp15* is expressed only in ovary. It is closely related to *Gdf9*, suggesting Bmp15 may be involved in oocyte maturation and follicular development as a homodimer or by forming heterodimers with Gdf9.[46] Missense mutations in *BMP15* have been identified in association with primary or secondary amenorrhea in several cohorts of women with POI.[28] The functional mechanism by which *BMP15* variants disturb ovarian function has not been defined. The clinical phenotype appears to be confined to the development of POI.

The development of large-scale medical sequencing has uncovered new genetic mechanisms causing POI in genes that affect the normal processes of primordial germ-cell proliferation and migration, oocyte meiosis, DNA repair and ovarian follicle formation/activation. Disruption of *SYCE1*, a gene involved in the early steps in chromosome synapsis and recombination during meiosis, is known to cause POI in mice.[47] Exome sequencing has associated pathological variation in this gene with POI in humans.[48] *HFM1* genetic variation has also been associated with human POI.[49] It is expressed exclusively in ovary and testis. It contains motifs suggesting a function in genome integrity in germline tissue. *STAG3* encodes a subunit of cohesin, a larger protein complex essential for proper pairing and segregation of chromosomes during meiosis. Exome sequencing has associated *STAG3* with human POI.[50]

Envirome

Evidence suggests non-genetic factors contribute about 90% of the risk of chronic disease.[51] Despite this, the vast majority of human exposures that might initiate disease processes have not been investigated. The envirome represents the totality of the environmental factors, both past and present, experienced by a person during life, which includes adverse socioeconomic conditions.[52] Taking an "envirome" perspective to health provides an avenue from which to fully integrate patient care and research. With regard to POI, evidence has associated cigarette smoking with an earlier age of menopause.[53] This is even true for exposure to secondhand smoke.[54, 55] Industrial exposure to 2-bromoprane in a cleaning solvent has been associated with the development of POI in 16 Korean women.[56] Endocrine-disrupting chemicals (EDC) have been associated with

earlier age of menopause. A cross-sectional survey using the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2008 examined 111 EDCs. EDC-exposed women were up to 6 times more likely to be menopausal than non-exposed women. The study identified 15 EDCs that warrant closer evaluation.[57]

Iatrogenic

Advances in the detection and management of cancers have resulted in considerable improvement in cancer survival. As young women and girls with malignancies become long-term survivors many experience temporary or permanent changes in ovarian function. Chemotherapeutics are also used in conditions other than cancer, such as for rheumatologic disorders.[58] The major factors influencing the degree of ovarian toxic effect of chemotherapy are the age of the patient at the time of treatment and the type, dose and duration of chemotherapy. Hematopoietic stem cell transplantation with cyclophosphamide treatment is associated with a high risk of POI. Methotrexate, fluorouracil, vincristine, bleomycin and dactinomycin have low risk of inducing POI.[59] Studies using gonadotropin-releasing hormone (GnRH) agonists to protect ovarian function during chemotherapy have shown mixed results and have lacked data on pregnancy outcomes. However, a recent controlled study showed that administration of goserelin with chemotherapy appeared to protect against POI and improve prospects for fertility.[60] Also, there are strategies in development to preserve fertility by other methods involving surgery and cryopreservation.[61]

Diagnosis

To make the diagnosis of POI in a timely manner the clinician must respect the menstrual cycle as a vital sign of health in girls and young women.[62, 63] Evidence supports a conclusion that many clinicians are failing in this regard.[8, 9] The most common presenting complaint of women with POI is a disordered menstrual cycle. This can be an abrupt cessation of menses, failure to resume menstruation after a pregnancy or stopping hormonal contraception, polymenorrhea, or dysfunctional uterine bleeding. Most commonly the patient presents with secondary amenorrhea after a prodrome of oligomenorrhea. In about 10% of cases the disorder presents with primary amenorrhea.[20]

Clinicians evaluating women with secondary amenorrhea, once pregnancy is ruled out, need to consider many possibilities. Is this an early sign of a decline in general health or an underlying condition? Is there inadequate caloric intake, excessive exercise or psychological stress? Is there prior radiation therapy or chemotherapy? Are there signs of androgen excess or galactorrhea? Four important causes of secondary amenorrhea are: 1) polycystic ovary syndrome; 2) hypothalamic amenorrhea; 3) hyperprolactinemia; and 4) primary ovarian insufficiency.[64]

Secondary amenorrhea should not be attributed to stress without further evaluation. After pregnancy is ruled out, the minimal laboratory evaluation of amenorrhea should include the measurement of serum prolactin, FSH, and thyrotropin levels.[64] In the case of hypothalamic amenorrhea related to stress, restricted caloric intake, or exercise, the serum FSH level will be in the low or normal range. If the FSH level is in the menopausal range, as defined by the reporting laboratory, this indicates POI. The FSH test should be repeated in 1 month along with a serum estradiol measurement.[17] The diagnostic criteria for POI are shown in Table I.[13]

Once the diagnosis of POI is confirmed a more detailed history and physical examination are in order. Are there other family members with POI? Are there autoimmune disorders in the family, such as hypothyroidism, adrenal insufficiency, or hypoparathyroidism? Is there a family history of fragile X syndrome or *FMR1*-related disorders such as intellectual disability, dementia, tremor or ataxia, or symptoms similar to those associated with Parkinson's Disease? Also, a more specific review of symptoms for the patient is in order once the diagnosis is made. The condition has been associated with adrenal insufficiency, hypothyroidism, dry-eye

TABLE I.—*Diagnostic criteria for primary ovarian insufficiency.*[13]

Age less than 40 years
Four or more months of disordered menses:
– Amenorrhea
– Oligomenorrhea
– Polymenorrhea
– Menometrorrhagia
Serum FSH:
– In the menopausal range as defined by the reporting laboratory
– On two occasions at least one month apart

TABLE II.—*Targeted physical examination after the diagnosis of primary ovarian insufficiency.*[13]

Stigmata of Turner syndrome:
– Short stature
– Webbed neck
– High, arched palate
– Increased carrying angle
Thyroid enlargement
Stigmata of adrenal insufficiency
– Hyperpigmentation
– Vitiligo

TABLE III.—*Indicated Examinations after the diagnosis of primary ovarian insufficiency.*[13]

To determine mechanism:
– Karyotype on 30 cells
– 21-hyroxylase autoantibodies by immunoprecipitation
– *FMR1* premutation status
As baseline evaluation:
– Pelvic ultrasound
– Bone mineral density
– Thyroid peroxidase autoantibodies

syndrome, myasthenia gravis, and systemic erythematosus.[65, 66] Physical examination may reveal other disorders: 1) stigmata of Turner syndrome such as short stature, webbed neck, and high, arched palate; 2) thyroid enlargement; 3) hyperpigmentation or vitiligo associated with adrenal insufficiency (Table II).[13]

The next order of business is to determine whether there is an identifiable mechanism of the POI. This is important because if a mechanism can be defined the patient can be monitored for other associated health risks. Is it Turner syndrome or a variant? A karyotype with counting of 30 cells is indicated to detect sex chromosomal mechanisms, to include 45,X mosaicism.[67] Is it autoimmune lymphocytic oophoritis (SCA-POI)? Testing for the presence of anti-adrenal antibodies is indicated to identify those women who have POI on the basis of autoimmune lymphocytic oophoritis. This is most readily assessed by measuring 21-hyroxlylase [CYP21] autoantibodies by immunoprecipitation.[19] Autoimmune lymphocytic oophoritis (SCA-POI) is the mechanism in only about 4% of women with POI. Is it FXPOI? Testing for a premutation in *FMR1* is indicated. Approximately 14% of women with a family history of POI and 2% of women with isolated POI will have FXPOI, *i.e.*, related to an *FMR1* premutation.[68] Measuring ovarian antibodies is not justifiable as they lack specificity.[69]

Certain pathogenic mechanisms of POI (such as isolated 17,20 lyase deficiency, aromatase deficiency and autoimmune lymphocytic oophoritis) are associated paradoxically with enlarged multi-follicular ovaries which are at risk of torsion. A baseline pelvic ultrasound is indicated in women with POI to identify the rare woman with this phenotype.[17] Hypogonadism is a recognized risk factor for reduced bone mineral density and osteoporosis. Therefore, girls and young women with POI should have a baseline bone mineral density measured at the time of diagnosis.[70] Because women with POI are at increased risk of Hashimoto thyroiditis, it is reasonable to measure thyroid autoantibodies at the time of diagnosis.[71] As mentioned, ovarian biopsy is not clinically indicated in the evaluation of POI (Table III).[20]

Management

Emotional health

Compared to controls, women with POI Score adversely on measures of anxiety and depression[72] and have an increased lifetime risk for major depression (Table IV).[69, 72] The most common words women with POI use to describe their emotional response to learning the diagnosis are "devastated," "shocked," and "confused".[73] This is a life-altering diagnosis, and raises existential issues regarding purpose in life. Infertility, a major disruptor of life plans, is associated with high levels of emotional distress.[74] When considering the diagnosis of POI it is best to have the patient schedule a return office visit to discuss the laboratory findings.

TABLE IV.—*Comparison of control women and women with spontaneous 46,XX POI with regard to frequency of mild, moderate, and severe depressive states.*[69]

Variable	POI (N.=98)	Controls (N.=60)	P-value
Depression (a)			
None (CES-D<16)	57 (58.8)	49 (81.7)	<0.002 (b)
Mild (CES-D 16-20)	14 (14.4)	6 (10.0)	
Moderate (CES-D 21-26)	8 (8.3)	2 (3.3)	
Severe (CES-D≥27)	18 (18.6)	3 (5.0)	
High anxiety (c) (STAI≥44)	37 (37.8)	5 (8.3)	<0.001 (d)

Values are number (percentage).
(a) Scores may range from 0 to 60, with higher scores reflecting greater depression; (b) Kruskal-Wallis Test for singly ordered contingency tables; (c) Scores may range from 20 to 80, with higher scores reflecting greater anxiety; (d) Fisher's Exact Test.

We hear from women that learning about this diagnosis over the telephone is particularly traumatic. How distressing news is delivered can have a profound effect on quality of life.[75]

Women with POI have lower self-esteem, increased shyness, and increased social anxiety compared to controls.[76] Evidence supports a role for a collaborative care model as a method to improve emotional health and medical outcomes, reduce costs, and also increase satisfaction for patient and clinician.[77] As indicated, collaboration with a social worker with special expertise in reproductive disorders, a psychologist, or spiritual care provider can help women with POI in their "quest for understanding life's ultimate questions and the meaning and purpose of living," one definition of the spiritual aspect of human existence.[78] Indeed, use of validated instruments has demonstrated functional well-being to be significantly and positively correlated with spiritual well-being and purpose in life in women with POI.[79] Women with POI who score higher on a validated measure of meaning and purpose have fewer symptoms of anxiety and depression, higher positive affect, and lower negative affect.[72] Evidence suggests clinicians can help women with POI improve their emotional well-being by: 1) informing them better about their condition, 2) helping them to feel less stigmatized by the disorder; and 3) assisting them in developing alternative goals with regard to family planning.[72]

Nutrition and lifestyle

Women with POI should be encouraged to maintain a healthy life style to optimize bone and cardiovascular health. Women with POI are at increased risk of fractures.[80] Cross-sectional studies of women with POI have shown the following factors to be significantly related to lower bone mineral density in these women: 1) inadequate physical activity; 2) inadequate calcium intake; and 3) lower serum levels of vitamin D.[70] Delay in diagnosis of POI also significantly contributes to reduced bone mineral density by delaying proper therapy. Women with POI are also at increased risk of mortality due to ischemic heart disease.[81-84] Familiarizing them with eating to avoid obesity, educating them about healthy food options to maintain cardiovascular health, undergoing appropriate screening for cardiovascular risk factors, instruction regarding foods rich in calcium (1200 mg daily), and guidance about vitamin D supplementation (800 IU daily) are important issues to address.

Preconception health

When pregnancy does occur in women with POI, it occurs unexpectedly. These women are especially joyful when this happens. They are certainly motivated to do everything possible to assure the best outcome. All women who might conceive should be made aware of the detrimental effects of alcohol and smoking on the fetus and inspired to make the needed changes.[85, 86] Foods rich in folic acid and folic acid supplementation reduce the risk of neural tube defects.[87] Preconception care is designed to identify and reduce biomedical, behavioral, and social risk factors to the health of a woman or her baby before pregnancy occurs.[88] It is mainly about optimizing their envirome. Women who could potentially become pregnant should be assessed for preconception risks and educated about the importance of maternal health in ensuring healthy pregnancies. Generally, few women present for preconception care. The US Preconception Health and Health Care Initiative has established a vision to prioritize preconception health.[89]

Hormone replacement

The goal of HRT in women with POI is to mimic normal ovarian function with regard to estradiol replacement. The average serum estradiol level during the menstrual cycle in normal women is approximately 100 pg/mL.[90] Transdermal or transvaginal replacement of 100 micrograms/day of estradiol achieves physiologic blood levels in this range and provides good symptomatic relief. The transdermal or transvaginal route is preferred because these are associated with a lower risk of vascular thromboembolism compared with oral estrogen.[91, 92] Evidence supports the addition of cyclical oral medroxyprogesterone acetate at the dose of 10 mg/day for 12 days each month. This regimen guards against the potential risk of endometrial hyperplasia and endometrial cancer by inducing full secretory endometrium and sloughing on a regular basis.[92, 93] Women with POI taking this regimen should keep a menstrual calendar and obtain a pregnancy test promptly if their menses

is late, and if positive stop the treatment. Data are not available regarding the endometrial effects of oral micronized progesterone when given in conjunction with a full replacement dose of estradiol.[94] Oral contraceptives are not recommended as first-line hormone replacement in women with POI because 1) they provide more steroid hormone than is needed for physiologic replacement and 2) are associated with an increased risk of thromboembolic events related to the first pass effect on the liver. A major advantage of transdermal and transvaginal estradiol replacement is the avoidance of this first pass effect on the liver. The American Society for Reproductive Medicine and the International Menopause Society have recommended HRT for women with POI.[64, 95] Studies regarding the risk of hormone therapy in menopausal women do not apply to young women with POI. Menopause is a physiologic condition, whereas POI is a pathologic condition in which women have low serum estradiol levels as compared with other women of similar age.[17]

Bone health

A recent controlled trial provides important evidence for women with POI and their clinicians. HRT regimens have been well-studied in postmenopausal women, but there has been limited research on the effects of these therapies on younger women with POI. The study followed bone mineral density over three years in a group of control women with normal ovarian function and a group of women with POI taking a standard HRT regimen (100 microgram/day estradiol patch, 10 mg per day oral medroxyprogesterone acetate for 12 days each month). When the study began women with POI had significantly lower bone densities than control women. By the study's end, bone density measurements in women with POI did not differ from the control group. The study demonstrated that not only could this regimen of HRT reduce the rate at which women with POI lose bone mineral density; it could actually restore bone density to normal.[96] This evidence from a prospective controlled study makes this regimen of HRT the standard by which to compare any other HRT regimen. Evidence suggests the cyclic nature of the HRT used is advantageous to bone health compared to using a continuous combined regimen. In one study oral continuous combined HRT (oral contraceptive) in women with POI did not increase lumbar spine bone mineral density as much as physiologic transdermal estradiol replacement. Also, the oral contraceptive regimen suppressed bone formation markers, whereas transdermal estradiol significantly increased bone formation markers.[97] Based on current evidence the preferred approach to HRT in women with POI is: 1) physiologic replacement of estradiol, by transdermal patch or vaginal ring; 2) cylic oral medroxyprogesterone acetate; and 3) a bone healthy lifestyle and with proper nutrition. Because of the uncertain effects of bisphosphonates on the fetus and their long skeletal half-life these agents are not recommended in women who might subsequently conceive.[98]

Endocrine health

Women with POI who test positive for adrenal autoimmunity, and thus have autoimmune lymphocytic oophoritis (SCA-POI) as the mechanism, have a 50% chance of subsequently developing adrenal insufficiency.[99] Patients with positive tests for adrenal antibodies should be evaluated annually by a corticotropin stimulation test. Longitudinal data are lacking with regard to how to manage women with POI who test negative for adrenal antibodies at the initial evaluation. Theoretically, one would expect adrenal-cell antibodies to be present at initial evaluation if the mechanism of the POI is steroidogenic cell autoimmunity. A reasonable strategy is to not repeat the testing unless it is otherwise clinically indicated. However, all patients with POI should be educated regarding the symptoms of adrenal insufficiency and should undergo evaluation of adrenal function if such symptoms develop. Since women with POI also have an increased risk of associated Hashimoto thyroiditis it is important to carefully monitor thyroid function as clinically indicated.[17]

Sexual health

A recent study compared sexual function in women with POI who were taking oral estrogen replacement with a control group of women without POI. Women with POI scored lower on sexual function than controls and experienced greater dyspareunia and complaints of inadequate lubrication.[100] However, women in this study were not using a physiologic replacement of trans-

dermal or transvaginal estradiol. A much larger study in which women with POI received a more physiologic replacement (100 microgram/day of transdermal estradiol and 10 mg/day oral medroxyprogesterone acetate for 12 days each month) showed that most women with POI had sexual function scores in the normal range while on replacement. However, as a group these young women scored significantly lower on the sexual function scale than control women.[101] Likelty multiple factors, including emotional and psychosocial ones, contribute to the reduced sexual function in women with POI.

Special situations

Adolescents

The diagnosis of POI is emotionally difficult and confusing for young girls and their families.[102, 103] A family systems approach may work best to navigate this situation. This approach considers the nuclear family as the emotional unit rather than one individual.[104] A health crisis impacting reproductive capacity in a child reverberates through the family. The problem must be addressed in this context.[105] It is important to realize adolescence encompasses a broad range of emotional maturity. One academic publication now in the public domain provides a starting point for parents and clinicians with "Tips and Tools for Talking: Helping Your Daughter Understand Primary Ovarian Insufficiency".[105] The goal of HRT during adolescence is to establish an age-appropriate hormonal milieu and appropriate development of secondary sexual characteristics, at an age consistent with the girl's peers.[106] Adolescents with POI benefit from learning to appreciate that families can come together in many different ways.

Turner Syndrome

Adults with Turner syndrome require continued monitoring of hearing and thyroid function, aortic enlargement, hypertension, diabetes, and dyslipidemia.[107, 108]

Oncofertility

Fertility impairment and loss due to cancer or its treatment is a significant consideration for many pediatric, adolescent, and young adult women.[109]

FXPOI

Several professional societies recommend that women with POI undergo testing for premutation in the *FMR1* gene,[110-112] Women who carry the *FMR1* premutation are at risk for fragile X associated tremor/ataxia syndrome and other medical, psychiatric and cognitive features and conditions.[113]

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

This is a rare autosomal recessive disease (also known as APS-1). It is caused by mutations of a single gene named Autoimmune regulator gene (*AIRE*). This causes a failure of T-cell immune tolerance. Central tolerance takes place within the thymus and represents the mechanism by which potentially auto-reactive T-cells are eliminated through the negative selection process. *Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy* (APECED) is characterized by several autoimmune endocrine and non-endocrine manifestations and the phenotype is often complex.[114]

Galactosemia

Despite early and lifelong dietary treatment, many patients with classic galactosemia go on to experience long term complications, including cognitive disability, speech problems, neurologic and/or movement disorders, and POI. There are currently diverse approaches for treating patients with this disorder. More extensive and statistically powerful research studies are needed to define best practices.[115]

Life plans

Contraception

The effectiveness of hormonal contraceptives has not been specifically studied in women with POI. There are reports of women with POI who have conceived while complying with an oral contraceptive regimen.[116] It may be oral contraceptives fail to adequately suppress the high FSH levels characteristic of POI. Women with POI who wish to avoid pregnancy should use a barrier method or possibly an intrauterine device.

Family building, traditional

The appropriate time for the clinician to provide guidance about building a family, by either traditional or technological methods, is after having established that the patient is endocrinologically healthy with regard to adrenal and thyroid function, and, importantly, adequately recovered emotionally from the news of the diagnosis. Presently no marker can predict which women with POI will conceive. No medical therapy has been definitively proven to improve ovarian function and fertility for these women. It is beneficial for women with POI to hear a balanced presentation about all life plan and family building options.[117] Child-free living is a choice for some women, and the preferred approach for a few. This must be respected. Adoption and foster children are good approaches for others. Some couples are averse to adoption and reproductive technologies and are content not to become parents, or to accept the low but real chance that the infertility will resolve spontaneously. Because ovarian function is intermittent and unpredictable in women with POI, attempts to time intercourse are not indicated. Couples who want to optimize their chances for conception should have intercourse two to three times a week to ensure that sperm are present should an ovulation occur (sperm can survive in a woman's genital tract for 3 days).[118] HRT induces regular menstruation but this does not mean that ovulation occurs on Day 14 of the induced cycle. Ovulations are still intermittent and unpredictable.

Family building, reproductive technology

The success of egg donation is primarily dependent on the age of the egg donor, so there is no medical urgency to proceed to egg donation. Rates of pregnancy with this method are similar among older and younger women.[119] There is some evidence to suggest egg donation is associated with a higher incidence of pregnancy complications, such as postpartum hemorrhage, small for gestational age, pregnancy-induced hypertension, and a minimal increase in the rate of birth malformations.[120-122] However, for most couples these risks are not of great enough magnitude to decide against the approach. Embryo donation has comparable results with egg donation and is less expensive.[123, 124]

The future

Design thinking

There are real-world problems needing solutions: 1) how do we close the knowledge-action gap to provide women and girls with POI the care they need? and, 2) how do we integrate research and patient care to improve research efficiency? These urgent needs provide focus and inspiration, which can accelerate innovation.[125] In the context of medical research and clinical care, the patient is the customer. A wider net is cast by effectively engaging the patient as a key collaborator in a design thinking process.

Mobile health, or Mhealth, has the potential to put patients in the center and empower them to improve their own care. Mhealth permits patients to share data about symptoms, treatments, and behaviors using smart phones or electronic tablets. These data can be used to create treatment plans specifically tailored to the patient's needs or to conduct research. Currently there are more than 40,000 medical mobile applications (apps) available for patients and clinicians. However, few are backed by clinical studies.[126] Medical apps have promise, but before integrating one into patient care and research it must be validated and proven effective.

By putting the patient at the center with a design thinking approach, Mhealth can help narrow the gap between knowledge and action. This gap is particularly a problem for those with a rare disease,[127] Viewed from this perspective, Mhealth has the potential to improve health equality. Health equality means everyone can reach their full health potential. Nobody is disproportionately disadvantaged in their health by living in a rural area, having a rare disease, low socioeconomic status, or other social determinants such as race. Health inequalities may be defined as systematic, unfair and avoidable inequalities.[128]

Ideally, for patients to be truly at the center, a community of patients with the disorder would be represented in decisions regarding the governance of care and research. Institutional Review Boards are charged with protecting individual patients in research matters. There is also a need to protect the interests of the community of women with POI. There is scant evidence regarding how to best engage a specific community of patients in governance. Community engagement involves collaborative partnerships. Shared leadership can build capac-

ity and create benefits to the community.[129, 130] Aspects of public health governance which could benefit from patient community engagement include: 1) policy development; 2) resource stewardship; 3) continuous improvement; and 4) partner engagement.[131]

POI can serve as one model rare condition from which to change the paradigm, to begin "Changing the Game" so to speak.[132] The approach will combine the potential power of Mhealth with the potential power of large-scale medical sequencing. The program will be governed by a not for profit organization led by women with POI.[7, 132] The effort is in harmony with the Patient-Centered Clinical Research network, or PCORnet, which is intended to advance real-time knowledge generation through the seamless integration of clinical practice and research.[133] The intent is to transform clinical care and research cultures from expert-centered and separate to patient-centered and integrated.

ConoverSystems.org, Inc. is a non-profit organization that has taken up this challenge. Their mission is to "empower and connect a community to advance the health and well-being of women and girls with POI." Their vision is "A world in which all women and girls achieve well-being and benefit from integrated personal health care".[134] ConoverSystems.org seeks to close the knowledge to action gap for girls and women with POI. They propose to do this by creating what they term a "Clinical Research Integration Special Program" for women and girls with POI.[7] The program will seamlessly integrate patient care and clinical research by putting the patient at the center of everything, transitioning the care and research model from "expert-centered" to "patient-centered." Large-scale medical sequencing provides the focal point around which to reorganize health care and health care research. No one clinician can be expected to master all the inherent nuances of genomic medicine and the management of rare diseases. There will be a need for digital tools that provide real-time clinical decision support to clinicians by integrating vast datasets. These tools will need to put patient needs at the heart of the effort with regard to communication and counseling. Mhealth provides the information and communication technology to bring all aspects of POI, care and research, into one domain, in real time, with the patient at the center (Figure 1).[1] The effort is best described as an "Integrated Health Research Alliance" for POI.

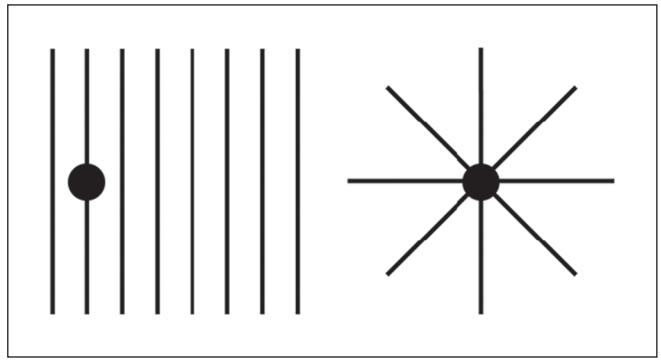

Figure 1.—A schematic diagram representing a reductionist versus integrated approach. The "expert-centered" approach is reductionist. In contrast, the "'patient-centered" approach is integrated. The patient is represented by the black circle. The different domains of expertise are represented by the lines. In the reductionist "expert-centered" model (left), research and patient care data are in one domain at a time. In the "patient-centered" model, research and patient care data are integrated into a single domain. Large scale medical sequencing and mobile health technologies provide driving forces to "change the game" to an integrated "patient-centered" system.[1]

The Internet and the advent of new digital channels such as social media, tablets, and smart phones has created a complex mix of technology by which to communicate. This has the potential to create multiple silos of information needlessly segregated from the enterprise as a whole. This makes resolving an issue in one contact

TABLE V.—*Comparison of systems designed to facilitate patient interactions in real time.*

System type	Characteristics	Advantages	Disadvantages
Single-channel	Single system	Simple	Limited functionality typically around administrative functions; no visibility into complex processes
Multi-channel	Multiple systems	Tailored systems for individual department's needs	System silos prevent bi-lateral information flow resulting in stovepipe planning and divergent processes
Cross-channel	Multiple systems	Systems "talk" to each other, information is shared as they are connected together; Convergent information flow	Limited information flow due to disparate system architecture; Complicated to administer
Omni-channel	Single system	Single overarching system of record with vary sub-applications meet complete functional needs; Maximum visibility into all aspects of care	Complex system with many stakeholders; Requires executive sponsorship to be effective

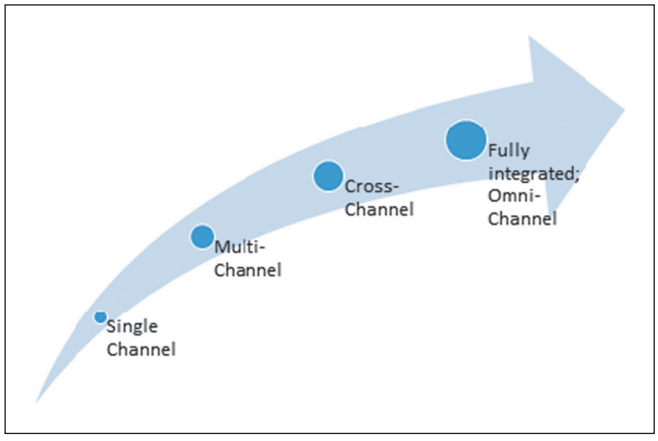

Figure 2.—A schematic representing the relative effectiveness of systems designed to handle patient interactions in real time.

quite challenging. There is a need to develop an omnichannel approach to health care and research Table V, Figure 2.[135]

Governance

An effective and stable alliance requires a robust governance structure. The structure must be capable of sustaining the effort through challenges and difficult times. Widely accepted research has shown that models of indigenous government were functioning quite successfully on the American continent when Europeans first arrived. The success of these indigenous governance models had significant influence on the framing of the US Constitution.[134] ConoverSystems.org is exploring a governance structure based on such egalitarian principles, respect for diversity, and representative democratic cooperation in the interest of the community as a whole.[136, 137] Seven women with POI have agreed to serve as "POI Tribal Elders" with an aim to represent the rights and interests of the international community of women with POI — the "POI Tribe." All seven of the POI Tribal Elders are women with POI who speak openly about their condition; all are committed to the mission and vision of Rachel's Well. The "Rachel's Well Primary Ovarian Insufficiency Community of Practice" is a group of volunteer experts covering a broad range of disciplines; it exists to provide medical, scientific, technical and management advice and counsel to the POI Tribal Elders.[138]

Community engagement

The word tribe arises from the Latin *tribus*, referring to one of the three original tribes of Rome, divisions of the Roman people. In this media-saturated world today, most strategies to engage community are built on persuading the masses through interruption, repetition, and constant presence. These are becoming less and less effective. A better approach is to target a specific community, or tribe, and puts focus on creating relevance and value for their specific needs.[139] By creating value for the individual and the specific tribe, one develops a sustained and rewarding presence to the community being served. In the case of ConoverSystems.org, their strategy focuses on the needs, goals, and aspirations of girls and women with POI. This type of engagement leverages affiliation, attracting tribal members with common traits. This approach suits the character and values of those involved; addresses desires for identity, self-expression, and membership. The approach also provides a social signal or status marker to empower the individual. This "patient-centered" tribal affiliation provides a strong sense of belonging to a group. The approach also creates ambassadors who spread positive word of mouth about the Rachel's Well initiative and the associated Integrated Health Research Alliance. Tribal engagement can deliver the most powerful messaging. The effort must be targeted to create value for participants, improve their experience, and constantly look for fresh ways to maintain relevance and create more value.

Computational modelling

Advanced analytical and computational tools can be combined to build quantitative networks of molecular and functional changes, occurring across multiple levels of biological organization.[140] These mathematical models can be combined with data (*e.g.* biomonitoring samples, 'omics screening, in vitro cellular toxicology, in silico structure-based predictions) to quantify the effects of environmental exposures and genetic variations on disease phenotypes. In the case of primary ovarian insufficiency, genome sequencing of patients, biomonitoring for environmental exposures, identification of molecular biomarkers, and research on the molecular mechanisms driving the pathophysiology will enable this type of a systems modeling approach, and in turn

facilitate prevention, early diagnosis, and treatment strategies.

Recent advances in computational power and high-throughput screening of human genetic, molecular, and cellular targets can be combined to build pathway based models. Such models link molecular initiating events to key cellular and tissue-level phenotypic changes, and ultimately to adverse outcomes. Such adverse outcome pathway network models have recently been developed and applied in the field of reproductive and developmental biology and toxicology. Examples include: 1) the identification of environmental exposures that may be linked to disruption of embryonic vascular growth and developmental defects;[141, 142] 2) modeling endocrine disruption via critical nuclear hormone receptor signaling;[143, 144] 3) connecting aromatase inhibition to female reproductive dysfunction in wildlife;[145] and 4) annotating molecular and gene networks related to human testicular dysgenesis syndrome.[146]

Integration

Integration involves making decisions that combine disparate and even opposing ideas. In its most basic form the process is about making space for new ideas and ways of thinking.[147] The community must share a sense of purpose, values and rules of engagement in order to integrate and continually innovate.[148] This glue holds things together when times get tough. Integrating diversity in itself is a strategy for innovation.[149] Culture trumps strategy every time, no matter how brilliant the plan.[150] Transforming an "expert-centered" system into a "patient-centered" system will require major change. It will require a change in culture. The "expert-centered" culture has functioned very well in many domains. ConoverSystems.org is working with, and within, this "expert-centered" culture to evolve positive change; change in the right direction benefits all and, in the end, will make sense to all. Today's best performing companies understand the need to avoid fighting existing culture. These types of organizations: 1) match strategy to culture; 2) focus on a few critical shifts in behavior; 3) honor the strengths of the existing culture; 4) identify "influencers" who can bring other employees along; 5) measure and monitor the cultural evolution.[141]

An innovative collaborative system for POI must encourage communication, ensure all claims about community are authentic, foster a feeling of solidarity, support acting fairly, and appeal to intrinsic motivations.[151] We favor an approach which engages and embraces human generosity rather than assuming people are purely driven by self-interest. Western culture has for generations based community models on the assumption that human beings are selfish at the core. In response, community models for the most part have focused primarily on monetary incentives, rewards, and punishments. Recent scientific evidence, as well as real world examples of community projects such as Wikipedia, open source software, and Craigslist, provide evidence that human beings are more cooperative and behave far less selfishly than we have long assumed. Systems based on cooperation rather than incentive are often more stable and successful. Evolution may actually favor people who collaborate, and societies that include such individuals.[151] When Lakota people pray together saying, "Mitakuye Oyasin," translated "All my relations," they embody and validate this approach to community.[152] In the final analysis, integration means making space for others who are different in culture and domain of expertise. This involves issues of rhetoric, friendship, authority, emotional space, and race.[153]

Conclusions

Most women with POI come to clinical attention with complaints of oligo/amenorrhea. To avoid delay in diagnosis this symptom must be taken seriously. In most cases the minimal laboratory evaluation of this symptom will be to test for pregnancy, and if negative, measure serum FSH, prolactin, and thyrotropin. Women meet criteria for POI if they are younger than age 40 years, have 4 months of oligo/amenorrhea, and two menopausal serum FSH levels 1 month apart. It is best to inform women of this diagnosis in person by a return visit in the office setting. The diagnosis is highly emotionally charged for young women. A sensitive and supportive approach is required. To determine the mechanism of POI once the diagnosis is confirmed requires the following tests: 1) karyotype analysis that counts 30 cells so as to uncover mosaic chromosomal abnormalities; 2) testing for the *FMR1* premutation; and 3) measurement of serum 21-hydroxlase auto-antibodies by immunoprecipitation. POI is more than infertility. Other aspects of physical and emotional health must be addressed before

moving on to plans for creating a family. Connecting community health providers in real time with a community of practice consisting of investigators who have the requisite knowledge and expertise would help close the knowledge to action gap women with this condition face regularly.

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